ACTA OPHTHALMOLOGICA
SUPPLEMENTUM 117

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AN ANALYSIS OF THE CORRELATION AND VARIATION OF PARAMETERS MEASURED FROM THE OPTIC CUP AND DISC IN 115 SUBJECTS

by

CARL HÅKAN JÖNSAS

MUNKSGAARD

COPENHAGEN 1972

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ACTA OPHTHALMOLOGICA
SUPPLEMENTUM 117

FROM THE DEPARTMENT OF OPHTHALMOLOGY
UNIVERSITY OF OULU
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OULU FINLAND

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PREFACE

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Tampere November 1972

Carl Håkan Jonsas

CONTENTS

INTRODUCTION 9

METHODS 13

- Equipment for stereophotogrammetry of fundus 13
- Measuring technique for stereophotogrammetry of fundus 17
- Reliability of measuring method 20
- Statistical methods 25
- Data processing 26

MATERIAL 27

RESULTS 28

- Correlations of characteristic ratios 28
- Characteristic ratios in different refraction groups 33
- Characteristic ratios in right and left eyes 42

DISCUSSION 43

SUMMARY 47

REFERENCES 50

INTRODUCTION

Stereophotogrammetry

Photogrammetry is concerned with the problem of determining with the aid of photographs the shape size and position of an object (Hallert 1964) In its modern form this technique was an innovation of the mid XIX th century when a Frenchman Colonel Laussedat began to use photographs for purposes of measurement Stereophotogrammetry an important branch of photogrammetry was originally developed for use in cartography and is nowadays applied in many other fields (Lacmann 1950) In medicine stereophotogrammetrical methods have been described e g by Lacmann (1950) and Bjorn et al (1954)

In stereophotogrammetry the object to be measured is first photo graphed from two different positions The photographs are then placed in a stereo device and by orientation brought into the same conditions as prevailed when the photographs were taken In examining the photos in the stereo instrument the observer receives from the stereoscopic effect of the difference in perspective a three dimensional impression of the object Stereoscopic vision depends on the two eyes seeing the same object independently at the same time each seeing it at a different angle from the other As this gives the brain the impression of seeing the object from two different sides the brain interprets the difference in the two images as distance The stereo instruments are constructed in such a way that in the three-dimensional coordinate system with moving space measuring marks the mathematical equations involved in the stereo photographing process are realised Use of the measuring marks is based on the fact that the separate marks are seen as a joined stereoscopic mark only when they are exactly located on the visual lines from the eyes of the observer to the point to be examined

Methods of measuring optic cup and disc

Previous authors have described various methods of obtaining data on the optic cup and disc The most usual technique for measuring the optic disc is direct ophthalmoscopy a simple and practical method

purpose In 1956 Krakau described another method likewise based on the coincidence principle in which a photographic double image is obtained with Nordenson s eye ground camera fitted with a stereo device The photographs were analysed and the protrusion measured with a self recording photometer The degree of exactness in both methods varied from 0 1 to 0 2 diopters There is also a photographic method of measuring the volume of papillary excavations or protrusions (Holm and Krakau 1970) A number of equidistant light sections of the disc are photographed and their area calculated The sum of the areas is proportional to the volume The coefficient of variation by this method is 5—10 % provided the media of the eye are clear

Crock and Parel (1969) published an account of the use of stereophotogrammetry in conjunction with stereoangiography to provide data for comparative analyses of changes in the posterior segment of the eye The authors made serial stereoangiograms of four patients using an automatic retinal camera and the stereo pairs were examined in a Wild A 5 universal stereo plotter The following pathological states were studied drusen of the optic disc vitelliform macular degeneration pailledema and retinal vascular webbing In 1970 Crock gave an excellent account of stereo technology in medicine He also described a procedure in which stereo pairs of fluorescein angiographs were processed in an analytical stereo plotter computer Functionally the system comprised a stereo comparator a digital electronic computer and an electronically controlled X Y coordinatograph Profiles and contours of optic cup and disc were calculated and illustrated

Oulu project for stereophotogrammetry of the eye ground

A project to apply stereotechnics in measurements of the fundus of the eye was initiated at the Eye Clinic of the University of Oulu in 1968 in collaboration with a private company which undertakes special photogrammetric commissions In 1969 Forsius et al presented the first results of the Oulu undertaking and drew attention to this new application of stereophotogrammetry in measurements of the eye ground

Aim of the present study

The aim of the present study was to develop a practical method of applying stereophotogrammetric techniques in the measurement of structures in the fundus of the eye The specific object was to study the size

and shape of the optic cup and disc in normal subjects of the same age and sex but with eyes of differing refractive states Normal variations in the optic cup and disc must of course be defined before pathological changes can be recognized

METHODS

Equipment for stereophotogrammetry of fundus

Camera

The stereoscopic photographs for the study were taken with a Zeiss automatic fundus camera to which an Allen stereoscopic separator was adapted (Allen et al 1966) As the ordinary fixation light in the Zeiss fundus camera proved unsuitable by reason of its size another fixation device with a very minute fixation point had to be constructed (Fig 1) In this new system the subject fixates with the same eye as the photograph represents The choice of photographed eye for fixation was to avoid the possibility of movements if orthophoria was disturbed In spite of the cycloplegia of the subject a stable fixation proved possible so that the position of the fundus could be reproduced in later photographs

Film

Photographs were taken on black and white Kodak Estar Base Panatomic X film, size 24×24 mm Developing was done with Agfa FINAL developer at 20°C for 6 minutes

Accuracy of photographic system

The total effect of the disturbances in the photographic system was investigated by taking test pictures of the bottom of an artificial test eye (see page 14) and measuring the pictures in the Zeiss PSK stereo comparator at the Helsinki University of Technology As the dimensions of the test eye were known the total photographic accuracy could be estimated Accuracy is affected by such errors as distortions in the optical system of the fundus camera regular and irregular dimensional changes in the film and the resolving power of the optics and the film The total accuracy expressed as the standard deviation of a measured image

A

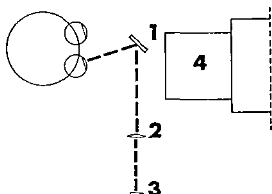
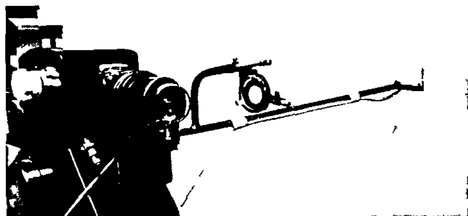


Fig 1 Fixation device constructed for the Zeiss fundus camera A Schematic representation of the fixation system 1 Mirror 2 Frame for correction lenses 3 Illuminated fixation point 4 Camera B Photograph of the fixation system

B

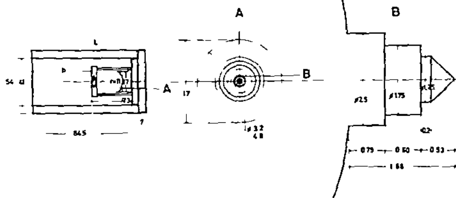


coordinate *proved better than ±0 015 mm This means* that *any linear* dimensions can be measured with an accuracy of ±0 02 mm Check was also made that the film in the fundus camera was plane Sevenfold magnification of grid photographs revealed no differences in graphical comparison The Zeiss fundus camera has no fiducial marks so that fixation and orientation of the pictures had to be made in relation to the mid points of the film edge The position of the mid point could be established to within 0 1 mm

Artificial test eye

Any applicable stereophotogrammetric method of determination presumes at least one absolute dimension to be known in the object Some dimension e g a length or a distance is necessary for the calculation of the scale between the object and the stereo model constructed with the

B



C

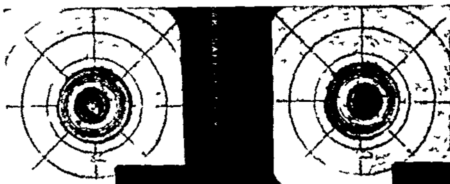


Fig 2 A Photograph of the test eye B Schematic representation of the test eye and the test figure and cup in its bottom The dimensions are expressed in mm *C Stereo photographs of the bottom of the test eye*

stereo photographs No means could be found here of marking a scale distance in the eye ground Another solution was therefore applied An artificial test eye (Fig 2) was constructed in which the optic cup was represented by a hollow turned out on the lathe The cup of the test eye was photographed with auxiliary lenses (L) The strengths of the lenses were 50 55 and 64 D respectively and the distance (a) of the forward surface of the lens from the bottom of the test eye could be varied from 16 8 to 27 8 mm By changing the strength of the lenses and the lens cup distances it was possible to simulate different refractive powers and axial lengths of the eyeball Many series of stereo photo graphs using these different lenses and distances were taken of the test eye and by means of a Wild A 4 stereo instrument measurements of the photographs were made using points on the walls of the test eye With these measurements an approximate scale applicable also for human eye measurements was calculated and scale correction coefficients based on the correspondence of convergence readings between human and test eye in the autograph were computed for later graphical and analytical application The stereo photographs taken of the test eye were also inter preted in the Zeiss PSK stereo comparator The comparator results were compared with those of the autograph Wild A 4 which was later utilized in practical interpretations of stereo photographs taken of the eyes of the subjects studied By these means the accuracy of the Wild A 4 could be calibrated Because complete correspondence of the test eye and the human eyes was not possible the use of relative values instead of absolute values was unavoidable and further clinical conclusions in this investigation were based on ratios of measured values

Wild A 4 autograph

In order to obtain measuring results available for computer processing the Wild A 4 (Fig 3) was equipped with temporary x y z coordinate scales The Wild A 4 measuring results were compared with the compa rator measurements In this comparison glass grid plates were used The plates were photographed with the fundus camera and measured with the Zeiss PSK stereo comparator and from the results obtained the distances between the points of intersection of the grid lines were meas ured After complete adjustment of the autograph the corresponding coor dinates were measured with it and the same distances were computed The average relative deviations between the two measurements of the

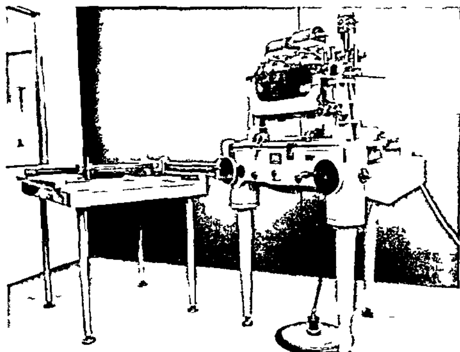


Fig 3 General view of the Wild A 4 autograph

respective distances was 0 0025 After this preliminary check of instruments stereo photographs were taken of the bottom of the artificial test eye furnished with a 55 diopter lens The coordinates of 16 symmetrically located points in each plane of the cup of the test eye were measured in four photographs by the stereo comparator and the autograph The measurements were compared with each other by transforming the Wild A 4 coordinates to the comparator coordinates system by Helmert transformation In this process the differences between the coordinates as residuals were calculated The comparator tests showed that with the autograph measurements an accuracy of 0 03 can be achieved. The tests also proved the Wild A 4 autograph accurate in measurements with various scales of stereo model Additional instrument tests were made to ensure that model distortions would not cause any considerable decrease in accuracy as the scales varied

Measuring technique for stereophotogrammetry of fundus

The stereoscopic pictures of the optic disc were taken for this study by the photographer at the Eye Clinic The correction lens of the camera

remained for all pictures at a constant adjustment of —16/+17 and the pictures were sharpened in the ordinary way by the camera objective The basis of the stereoscopic separator was set at 2 5 mm Mydriasis and cycloplegia were induced by 1 % Cyclopentolate (Cyclogyl®) instilled three times at five minute intervals thirty minutes before photographing

As there were no fiducial marks in pictures taken with the fundus camera the operator had to mark the mid point of each border before the photograph was placed in the autograph The picture could then be oriented in the Wild A 4 with the aid of its own grid pattern convexity of the film being eliminated by compression between optic glasses The grid lines were useful in that if measurement of the mid point of the developed film was inaccurate the error could be checked in the enlargement and corrected immediately In orientation it could also be established with the aid of the parallax of the stereo measuring marks whether the film was firmly pressed against the grid plate If the eye had clearly moved between the two successive exposures a strong parallax was created and the pictures could not be satisfactorily oriented With this possibility in mind each eye was photographed at least three times to provide a sufficient range of pictures from which to select the best stereo pairs

For the purposes of data processing special forms were provided on which the operator could record the x z and y coordinates of the measured points of the eyes. The procedure adopted in stereo interpretation was as follows The operator commenced measurement from the uppermost closing contour of the optic cup next the optic disc and the section of the optic cup on the plane of the disc together with the sections of the optic cup where its form changed In addition the depth of the cup was measured. In some of the photographs this was extremely difficult and three stereo pairs were omitted from the material because the operator in fact failed to locate the bottom by reason of its transparency Another matter which caused difficulties in interpretation was that the edge of the disc is covered by the fibre layer If the operator felt that some point on the edge could not be measured he would place a question mark on the form instead of the coordinates of the point In such cases the curve passing through the three nearest points was calculated in further data analysis by means of a computer programme In addition the location of the uppermost point of the retinal nerve fibre layer was recorded In general four sections were used to determine the shape of the optic cup Fig 4 shows contours and profiles of the cup

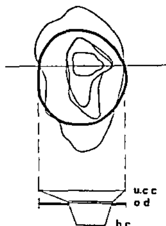


Fig 4 A Contours of the optic cup and disc in the left eye of a subject. Below Profile constructed from the contours u c.c. = uppermost closing contour of the cup o d = optic disc b c. = bottom of the cup B Stereo photographs of the same eye



and disc in the left eye of a subject Since in the pictures it proved possible to obtain a stereoscopic view of the walls and the bottom of the cup the central axis of the cup must be almost parallel with the axis along which the pictures were taken At interpretation some of the orien ted stereo models had vertical parallaxes Because of parallax difficulties 11 stereo pairs were omitted from the material Scale differences in the stereo pairs in the study were eliminated in that when a stereo model had been interpreted in the autograph the operator selected from the tables the scale correction coefficients characteristic for each contour Thus the Wild A 4 coordinate measurements were analytically reduced by the coefficients and the results were comparable with each other at the data processing stage

Reliability of measuring method

To estimate the reliability of the measuring procedure developed in this study the right eyes of ten test subjects were photographed each twice on different occasions In the same way three additional subjects were photographed each three times on different occasions The following quantities (Fig 5) for each eye were computed from the Wild A 4 measurements

Symbol	Quantity
h_c =	height of cup to uppermost closing contour
h_d =	height of cup to plane of disc
h_n =	highest point of nerve fibre layer measured from plane of upper most closing contour
a_c =	area of cup on plane of disc
a_d =	area of disc
m_c =	mean area of cup
m_d =	mean area of cup below plane of disc
v_c =	volume of cup
v_d =	volume of cup below plane of disc

A computer program specially prepared for this study was used in the calculations of ratios between the above quantities the diameter of the optic disc being used as scale segment Because the measured values represented quantities of various types e g length area and volume the values of areas were transformed into circle diameters of the same area this technique was chosen because the diameters of the cup and disc are easy to observe and measure — the values of volumes were transformed into the cube root of the volume this technique is best applicable when the shape is not known in detail

Generally the confusion involved in dealing with mixed quantity types is avoided as explained above by transforming the measured values into linear quantities

The area bounded by closing contours was worked out as follows Ten new points were calculated between each two successive measured points For this purpose an interpolation technique was evolved giving a curve

and derivative which are continuous The area of the resulting polygon was worked out by the usual polygon method

The volume of the cup was calculated according to the formula

$$v = \int_{h_b}^{h_p} A(y)dy$$

where y is the height and A(v) the area of the cup at the height v h_p and h_b being the y values of the uppermost closing contour and the bottom of the cup respectively

The mode of application of the formula was to calculate the volumes by adding together the volumes of truncated cones whose bases were formed by successive contours

The mean area of the cup was calculated by dividing the volume of the cup by its height

To define reliability of the measurement system the concept of mean error d was adopted

$$d = \frac{1}{N} \sum_{i=1}^{N} d_i$$

where i refers to the ith sample N is the number of eyes and d_i is the arithmetic mean of relative deviations in a sample i e

$$d_i = \frac{1}{n} \sum_{j=1}^{n} \frac{|x_j m_x|}{m_x}$$

In the formula j refers to the jth observation in the sample and m_x to the arithmetic mean of the sample The number of observations in a sample is n A sample consists of the measurements of one eye

The mean error concept was compared with the standard deviation concept generally used in statistics The mean error concept was preferred in this study in estimating the reliability of the measuring procedure because it makes it possible to use relative errors (variation coefficients) at an early stage in the calculation thus taking into account

the individual variations of the parameters calculated from the cup and disc

The mean errors of the quantity ratios are given expressed as percentages in Table 1

TABLE 1 Mean errors of quantity ratios of test material expressed in percentages

ratio	d [%]	ratio	d [%]
m_c/m_d	15.5	m_c/a_d	11.4
m_c/h_n	26.0	m_c/a_c	12.1
m_c/h_c	17.3	m_c/h_d	20.6
m_c/v_c	16.8	m_c/h_v	27.6

ratio	d [%]	ratio	d [%]
m_d/a_d	10.0	m_d/h_n	33.0
m_d/a_c	6.7	m_d/h_c	18.9
m_d/h_d	16.1	m_d/v_c	19.0
m_d/v_d	14.6		

ratio	d [%]	ratio	d [%]
a_d/h_n	30.6	a_d/a_c	3.7
a_d/h_c	16.8	a_d/h_d	14.6
a_d/v_c	19.0	a_d/v_d	22.0

ratio	d [%]	ratio	d [%]
h_n/a_c	31.7	h_n/h_c	22.0
h_n/h_d	29.1	h_n/v_c	20.2
h_n/h_d	35.9		

ratio	d [%]	ratio	d [%]
a_c/h_c	18.6	a_c/h_d	15.6
a_c/v_c	20.4	a_c/v_d	20.3

ratio	d [%]	ratio	d [%]
h_c/h_d	7.8	h_c/v_c	11.8
h_c/v_d	16.4		

ratio	d [%]	ratio	d [%]
h_d/v_c	17.3	h_d/v_d	10.9

ratio	d [%]
v_c/v_d	21.5

On the basis of this test material a number of characteristic ratios of the cup and disc were chosen and for the whole material the following characteristic ratios were subsequently calculated m_c/a_d m_c/a_c m_d/a_d m_d/a_c a_c/a_d h_d/h_c h_c/v_c and h_d/v_d The ratios are formulated so as to give a magnitude of 1 or less than 1

From the test eye measurements the mean errors of the corresponding characteristic ratios were also calculated The mean errors from three different measurements of the test eye are shown in Table 2

Factors affecting reliability

The preliminary investigation showed that the most accurate results came from those autograph measurements in which quantities on the same

TABLE 2 *Mean errors of characteristic ratios from measurements of the test eye expressed in percentages*

ratio	d [%]	ratio	d [%]
m_c/a_d	1 4	a_c/a_d	0 3
m_c/a_c	2.2	h_d/h_c	0 8
m_d/a_d	1 3	h_c/v_c	1 7
m_d/a_c	2.1	h_d/v_d	2.0

x z plane — e g diameter of cup and diameter of disc — were compared The mean error for the cup/disc (a_c/a_d)ratio was 3 7 % and in measurement of the test eye the corresponding value was 0 3 % The preliminary examination also revealed that results were better in the x z-direction than in the y direction This is due to the absence of clearly defined points in the y-direction i e the depth direction of the cup for there were difficulties in estimating just where the measuring mark reached the eye ground The results obtained also correspond to those in aerial mapping where accuracy of altitude measurement is clearly poorer than planimetric accuracy

As in all photogrammetric work picture quality is of the utmost importance for accurate measurement Especially where the surface of the retina is transparent exposure and sharpness of image are decisive factors The placing of the measuring mark in the y-direction is particularly difficult because the outermost layer of the retina the nerve fibre layer is transparent This is seen in the results in the poor mean errors of ratios

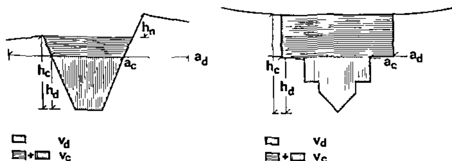


Fig 5 Schematic representation of the quantities calculated from the optic cup and disc and of the corresponding quantities calculated from the test eye

where the height of the nerve fibre layer (h_n) is a nominator or denominator Likewise while the walls of the cup presented no great problems of interpretation the operator found it difficult to estimate the bottom of the cup in the y direction Bearing this in mind it is surprising that the mean errors for the ratios h_d/h_c h_c/y_c and h_d/y_d were as low as 7 8% 11 8% and 10 9% The mean errors of the corresponding ratios of the test eye were 0 8% 1 7% and 2 0% The mean errors of the ratios m_d/a_d m_c/a_d m_d/a_c and m_c/a_c (10 0% 11 4% 6 7% and 12 1%) were relatively good because as noted above it is easier to measure with the autograph in the x,z direction than in the y direction and it was also easier for the operator to interpret points on the walls of the cup The mean errors of the corresponding ratios calculated from the test eye were 1 3% 1 4% 2 1% and 2 2%

The stereophotogrammetric method applied in measuring the artificial test eye meant an accuracy of characteristic ratios of 2 2% or better Assuming that equally measurable pictures could be obtained from the eye ground as from the test eye the reliability of the measuring method should be of the same class for the human eyes as for the test eye This was not the case however The mean errors of the characteristic ratios of the optic cup and disc were now 3 7—12 1% The main reason for the discrepancies between the human eye and test eye measurements was that the operator had considerable difficulties in interpreting the stereoscopic model of the tissues in the eye ground Although the stereo pairs of the eye ground were of good quality differences in darkness between the right and left pictures were slightly disturbing For this reason every effort should be made to equalise the brightness of the photographs at the printing stage Equalisation of light conditions in the stereo equipment is possible but may not produce the same results as careful development Another facto hindering interpretation was the difficulty in orienting the pictures in the absence of fiducial marks For future sterophotogrammetric studies the fundus camera should be equipped with fiducial marks and a camera affording the possibility of simultaneous exposures though not easy to construct would also be a great asset In the present study the focal length of the Zeiss fundus camera was not known and could not be satisfactorily ascertained When data on the focal length of camera and stereo plotter are available the scale of the stereo model can be better determined Possible reading errors by the operator or errors incurred at the coding stage can be eliminated when the autograph is furnished with devices for automatic registration

Statistical methods

Except for the concept of mean error specially adopted for this study current statistical methods were used

The mean value m_x was calculated by means of the usual formula

$$m_x = \frac{1}{N} \sum_{i=1}^{N} x_i$$

where x is a variable and N the number of observations

The standard deviation s_x was found from the formula

$$s_x = \sqrt{\frac{\sum_{i=1}^{N} (x_i - m_x)^2}{N-1}}$$

The correlation coefficient r_{xy} between variables x and y was calculated from the formula

$$r_{xy} = \frac{\frac{1}{N} \sum_{i=1}^{N} \left[(x_i - m_x) \ (y_i - m_y) \right]}{s_x \ s_y}$$

The coefficients were tested by t test using the expression

$$t = \sqrt{\frac{N-2}{1-r_{xy}}} \, r_{xy}$$

which follows Student t distribution with N — 2 degrees of freedom

If the significance level was $< 0.1\%$ the result was regarded as highly significant If it was $< 1\%$ but $\geq 0.1\%$ it was regarded as significant If it was $< 5\%$ but $\geq 1\%$ it was regarded as probably significant

The regression model of the variable y predicted by x was

$$y = a + bx$$

The regression coefficient b was calculated according to the formula

$$b = \frac{\sum_{i=1}^{N} \left[(x_i - m_x) \quad (y_i - m_y)\right]}{\sum_{i=1}^{N} \left[(x_i - m_x)^2\right]}$$

and constant term a is

$$a = m_y - bm_x$$

The significance of the difference between the means of two samples was determined by t test

$$t = \frac{m_{x_1} - m_{x_2}}{\sigma \sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} \quad \text{where}$$

$$\sigma = \sqrt{\frac{N_1 s_{x_1} + N_2 \quad s_{x_2}}{N_1 + N \quad - 2}}$$

The subscripts refer to samples m_{x_1} and m_x are the sample means s^2_1 and s^2 the variances and N_1 and N_2 the sample sizes

Data processing

The data from the observation forms were coded and punched into cards Thence they were transferred to magnetic discs which constituted input units in processing Stereo operators identification errors and typists coding errors were checked by means of an auxiliary input program and by drawing the contours of the cup and disc by the plotter in the data processing phase The plotter pictures were then compared with the corresponding stereo pictures

Computer processing was mainly carried out in the Institute of EDP University of Oulu Statistical analyses were made using statistical library programs (Honeywell) in Oulu University and the statistical data pro cessing system SURVO in the University of Tampere

MATERIAL

The material consisted of 158 healthy males aged 18—24 years The selection was intended to make the material independent of the age and sex factors The subjects had a refraction range from sphere +7 25 diop ters to —6 75 diopters and a maximum astigmatism of 1 0 diopter

In noting medical histories attention was paid to diseases possibly affecting the optic disc If any such disease was revealed the subject was excluded from the material To the same end all persons were subjected to a routine ophthalmological examination to rule out the possibility of disease Visual acuity with and without correction was tested Objective determination of refraction was made in cycloplegia using a Copeland streak retinoscope Biomicroscopy was carried out with a Haag Streit slit lamp and intraocular pressure was measured by means of a Gold mann applanation tonometer Ophthalmoscopy was performed during cycloplegia in order to rule out any disease or abnormality of the optic disc Special interest centred on the configuration of the disc and the presence or absence of physiologic excavation The presence of spon taneous venous pulsation was noted Visual field was tested using a Gold mann perimeter The blind spot was also checked on a Bjerrum screen

In subjects with a refraction range from ± 0 to +1 0 diopter both eyes were investigated but in all other subjects only the right eye was subjected to stereophotogrammetrical examination

A total of 30 eyes had to be excluded from the material by reason of imperfections in the photographs three because the operator failed to locate the transparent bottom of the cup and one eye as a consequence of ocular anomaly In nine eyes the bottom of the cup was located above the plane of the disc As a result the characteristic ratios could not be calculated for these eyes

RESULTS

With regard to the eyes included in the present material mean values standard deviations regression lines correlations and t values for correlations were calculated for the characteristic ratios h_d / h_c m_c / a_d, m_d / a_c $h_d / {}_d$ h_c/v_c m_c/a, a_c/a_d m_d/a_d for refraction and applanation pressure In addition the differences of mean values of the ratios were tested by t test in different refraction groups The material was divided into five refraction groups Group R_1 consisted of eyes with a refraction exceeding —3 0 D Group R comprised the rest of the myopic eyes with refraction of —3 0 D or below R_3 consisted of eyes with a refraction ranging from ±0 to +1 0 D and R_4 contained the hyperopes with a refraction of over +1 0 D up to +4 0 D Group R_5 was made up of eyes with a refraction above +4 0 D In addition the percentage frequency distribution of the characteristic ratios in the five refraction groups and in the whole sample was worked out In nine eyes (6 1 % of the total number of eyes) the bottom of the cup was located above the plane of the disc and therefore the characteristic ratios could not be calculated Of these eyes three belonged to group R_1 and two each to groups R R_3 and R_5

In this study the characteristic ratios refraction and applanation pressure were used as variables

Correlations of characteristic ratios

Correlations of variables calculated from the whole data are presented in Table 3 The most significant non trivial linear dependencies were also subjected to regression analysis

TABLE 3 *Correlations of variables calculated from the whole data*

VARIABLES	h_d/h_c	m_c/a_d	m_d/a_c	h_d/v_d	h_c/v_c	m_c/a_c	a_c/a_d	m_d/a_d	Ref	P_A
h_d/h_c	1 000									
m_c/a_d	—0 101	1 000								
m_d/a_c	0 080	0 234	1 000							
h_d/v_d	0 350	—0 006	0 030	1 000						
h_c/v_c	0 300	0 006	0 056	0 956	1 000					
m_c/a_c	—0 642	0 322	—0 047	—0 199	—0 224	1 000				
a_c/a_d	0 601	0 420	0 012	0 113	0 131	—0 544	1 000			
m_d/a_d	0 456	0 625	0 741	0 125	0 190	—0 102	0 548	1 000		
Ref	0 015	—0 059	—0 030	0 056	0 042	0 084	—0 115	—0 066	1 000	
P_A	0 136	—0 053	—0 104	0 061	0 074	—0 164	0 208	—0 010	0 114	1 000

Relations between characteristic ratios

Relation between h_d / h_c and a_c / a_d
Regression model $h_d / h_c = 0\ 383 + 0\ 601\ a_c / a_d$
Regression variance = 0 3607
Residual variance = 0 6393
Significance level = 0 001
The linear dependency is highly significant The h_d / h_c ratio can be explained with the regression model to the extent of 36 %

Relation between h_d / h_c and m_c / a_c
Regression model $h_d / h_c = 0\ 855 - 0\ 642\ m_c / a_c$
Regression variance = 0 4117
Residual variance = 0 5883
Significance level = 0 001
The linear dependency is highly significant The h_d / h_c ratio can be explained to the extent of 41 % with the regression model

Relation between m_c / a_d and m_d / a_c
Regression model $m\ / a_d = 0\ 083 + 0\ 234\ m_d / a_c$
Regression variance = 0 0546
Residual variance = 0 945
Significance level = 0 01
The linear dependency is significant Here the m_c / a_d ratio can be explained by means of the regression model to the extent of 5 %

Relation between characteristic ratios and applanation pressure

A positive correlation between a_c / a_d and applanation pressure (P_A) was found

Relation between a_c / a_d and applanation pressure
Regression model $a_c / a_d = -2\ 001 + 0\ 207\ P_A$
Regression variance = 0 0431
Residual variance = 0 9569
Significance level = 0 02

The linear dependency is probably significant The a_c / a_d ratio can be explained with the regression model to the extent of 4 %

Relation between characteristic ratios and refraction

No significant correlation between the characteristic ratios and refraction was found However since the clinical impression has been that there is some correlation between the size of the cup and refraction the four highest linear dependencies were demonstrated by regression analysis

Relation between a_c / a_d and refraction
The relation is seen in Fig 6
Regression model $a_c / a_d = 0\ 513 - 0\ 00615$ Ref
Regression variance = 0 0012
Residual variance = 0 9987
Not significant

Relation between m_c / a_d and refraction
The relation is seen in Fig 7
Regression model $m_c / a_d = 0\ 119 - 0\ 00063$ Ref
Regression variance = 0 0041
Residual variance = 0 9958
Not significant

Relation between m_d / a_d and refraction
The relation is seen in Fig 8
Regression model $m_d / a_d = 0\ 091 - 0\ 00106$ Ref
Regression variance = 0 0032
Residual variance = 0 9968
Not significant

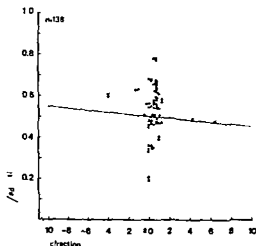


Fig 6 Relation between a_c/a_d (area of cup on plane of disc area of disc) ratio and refraction The correlation is not significant

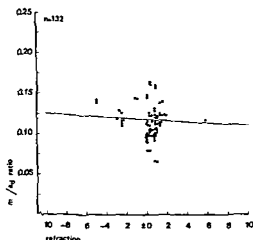


Fig 7 Relation between m_c/a_d (mean area of cup/area of disc) ratio and refraction The correlation is not significant.

Relation between m_c / a_c and refraction

The relation is seen in Fig 9

Regression model $m / a_c = 0.264 + 0.00390$ Ref

Regression variance = 0.003

Residual variance = 0.997

Not significant

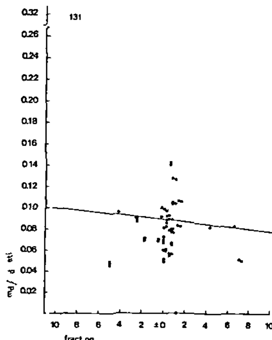


Fig 8 Relation between m_d/a_d (mean area of cup below plane of disc/area of disc) ratio and refraction The correlation is not significant

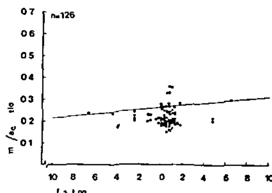


Fig 9 Relation between m_e/a_e (mean area of cup/area of cup on plane of disc) ratio and refraction The correlation is not significant

Obvious relations

In Table 3 some correlations are trivial despite the fact that the regression is significant because the dependency is obvious An example of an obvious regression is the relation between the h_d / v_d and h_e / v_e

Regression model $h_d / v_d = 0.061 + 0.956\, h_e / v_e$

Regression variance = 0 9137

Residual variance = 0 0863

Significance level = 0 001

The linear dependency is highly significant The h_d/v_d can be explained by means of the regression model to the extent of 91 % However it is evident that there is dependency because h_1 and v_d are subsumed in h_c and v_e as shown in Fig 5

Characteristic ratios in different refraction groups

Frequency distributions

In the following the percentage frequency distributions of the character istic ratios in the five refraction groups and in the whole sample are presented In the tables the frequency is expressed as a percentage instead of an absolute number to permit comparison of the variables From the frequency distribution tables below some numerical information has been picked out in order to find typical ranges of the characteristic ratios and significances

The percentage distribution of the h_d/h_c ratio in the different refraction groups and in the whole sample appears in Table 4

TABLE 4 *Percentage frequency distribution of h_d/h_c (height of cup to plane of disc/height of cup to uppermost closing contour) ratio in refraction groups R_1 R R_3 R_4 R_5 and in the whole sample*

h_d/h_c RATIO	REFRACTION (D) R (−3>Ref)	R (−3≤R f<±0)	R (±0≤R f≤+1)	R (+1<Ref≤+4)	R (Ref>+4)	TOTAL
≤ Ratio ≤0 1	0 0	0 0	2 8	6 3	0 0	2.2
1< Ratio ≤0 2	0 0	0 0	0 0	0 0	0 0	0 0
2< Ratio ≤0 3	0 0	0 0	4 2	0 0	13 3	3 6
3< Ratio ≤0 4	23 1	4 4	2 8	0 0	0 0	4 4
4< Ratio ≤0 5	15 4	13 0	8 5	6 3	6 7	9 4
5< Ra io ≤0 6	15 4	13 0	8 5	12.5	20 0	11 6
6< Ratio ≤0 7	0 0	21 7	14 1	25 0	33 3	17 4
7< Ratio ≤0 8	30 8	26 1	15 5	6 3	20 0	18 1
8< Ratio ≤0 9	7 7	17 4	28 2	25 0	0 0	21 0
9< Ratio ≤1 0	7 7	4 4	15 5	18 8	6 7	12.3
NUMBER OF EYES	13	23	71	16	15	138

In all the myopic eyes the h_d / h_c ratio is more than 0 3 whereas in the emmetropic and hyperopic eyes h_d / h_c ratios of 0 3 or below can be found In group R_5 (Ref $>$ +4 0) there is a smaller percentage of high h_d / h_c ratios (0 7—1 0) than in the other groups 80 % of all eyes have h_d / h_c ratios between 0 5 and 1 0

The percentage distribution of the m_c / a_d ratio (Table 5) and the m_d / a_c ratio (Table 6) is fairly similar In 99 3 % of the eyes the range of values for the m_c / a_d ratio is 0 2 or below and for the m_d / a_c ratio the range is 0 2 or below in 97 % of the eyes

TABLE 5 *Percentage frequency distribution of m_c/a_d (mean area of cup/area of disc) ratio in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

m_c/a_d RATIO	REFRACTION (D) R (−3>Ref)	R_2 (−3≤Ref<±0)	R (±0≤Ref≤+1)	R (+1<Ref≤+4)	R (Ref>+4)	TOTAL
0≤ Ratio ≤0 05	0 0	0 0	8 5	6 3	0 0	5 1
0 05< Ratio ≤0 1	7 7	17 4	25 3	6 3	20 0	19 5
0 1< Ratio ≤0 15	84 6	73 9	52.1	87 6	66 7	64 5
0 15< Ratio ≤0 2	7 7	8 7	12 7	0 0	13 3	10 2
0 2< Ratio ≤0 25	0 0	0 0	1 4	0 0	0 0	0 7
NUMBER OF EYES	13	23	71	16	15	138

TABLE 6 *Percentage frequency distribution of m_d/a_c (mean area of cup below plane of disc/area of cup on plane of disc) ratio in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

m_d/a_c RATIO	REFRACTION (D) R (−3>Ref)	R_2 (−3≤Ref<±0)	R_3 (±0≤Ref≤+1)	R (+1<Ref≤+4)	R_5 (Ref>+4)	TOTAL
0≤ Ratio ≤0 05	0 0	0 0	13 6	6 3	0 0	7 6
0 05< Ratio ≤0 1	0 0	4 4	6 0	0 0	0 0	3 8
0 1< Ratio ≤0 15	0 0	13 0	18 2	6 3	20 0	14 3
0 15< Ratio ≤0 2	100 0	82 6	56 0	87 6	80 0	71 4
0 2< Ratio ≤0 25	0 0	0 0	6 1	0 0	0 0	3 0
NUMBER OF EYES	13	23	66	16	15	133

The percentage distribution of the ratios h_d / v_d and h_e / v_e appears in in Tables 7 and 8

TABLE 7 *Percentage frequency distribution of h_d/v_d (height of cup to plane of disc/volume of cup below plane of disc) ratio in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

h_d/v_d RATIO	REFRACTION (D) R (−3>Ref)	R (−3≤Ref<±0)	R (±0≤R f ≤+1)	R_4 (+1<R f≤+4)	R (Ref>+4)	TOTAL
Ratio ≤0 1	0 0	0 0	18 3	12.5	0 0	10 9
< Ratio ≤0 2	0 0	0 0	0 0	0 0	0 0	0 0
< Ratio ≤0 3	8 3	0 0	4.2	0 0	0 0	2.9
< Ratio ≤0 4	0 0	12 5	2.8	6 3	6 7	5 1
< Ratio ≤0 5	8 3	16 7	2.8	6 3	0 0	5 8
< Ratio ≤0 6	25 0	20 8	2.8	25 0	20 0	12.3
< Ratio ≤0 7	16 7	25 0	8 5	25 0	20 0	15 2
< Ratio ≤0 8	8 3	8 3	2.8	12 5	26 7	8 0
< Ratio ≤0 9	8 3	4 2	4.2	12.5	0 0	5 1
< Ratio ≤1 0	0 0	4 2	5 6	0 0	6 7	4 4
< Ratio ≤2 0	25 0	8 3	28 2	0 0	13 3	19 6
< Ratio ≤3 0	0 0	0 0	9 9	0 0	6 7	5 8
< Ratio ≤4 0	0 0	0 0	4 2	0 0	0 0	2.2
< Ratio ≤5 0	0 0	0 0	5 6	0 0	0 0	2.9
NUMBER OF EYES	13	23	71	16	15	138

The distribution of group R_3 shows a great range of ratio values be cause of the large number of samples in this group 70 % of the h_d / v_d ratios and 72 % the h_e / v_e ratios have a range from 0 0 to 1 0 and the remaining 30 % and 28 % a range from 1 0 to 5 0

The percentage distribution of the m_e / a_e ratio (Table 9) is almost the same in all refraction groups 89 % of the eyes show an m_e / a_e ratio between 0 1 and 0 4 and no ratios above 0 7 are found

In all the myopic eyes the h_d / h_c ratio is more than 0 3 whereas in the emmetropic and hyperopic eyes h_d / h_c ratios of 0 3 or below can be found In group R_5 (Ref > +4 0) there is a smaller percentage of high h_d / h_c ratios (0 7—1 0) than in the other groups 80 % of all eyes have h_d / h_c ratios between 0 5 and 1 0

The percentage distribution of the m_c / a_d ratio (Table 5) and the m_d / a_c ratio (Table 6) is fairly similar In 99 3 % of the eyes the range of values for the m_c / a_d ratio is 0 2 or below and for the m_d / a_c ratio the range is 0 2 or below in 97 % of the eyes

TABLE 5 *Percentage frequency distribution of m_c/a_d (mean area of cup/area of disc) ratio in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

m_c/a_d RATIO	REFRACTION (D) R (—3>Ref)	R_2 (—3≤R f<±0)	R (±0≤Ref ≤+1)	R_4 (+1<Ref≤+4)	R (Ref>+4)	TOTAL
0≤ Ratio ≤0 05	0 0	0 0	8 5	6 3	0 0	5 1
0 05< Ratio ≤0 1	7 7	17 4	25 3	6 3	20 0	19 5
0 1< Ratio ≤0 15	84 6	73 9	52 1	87 6	66 7	64 5
0 15< Ratio ≤0 2	7 7	8 7	12 7	0 0	13 3	10 2
0 2< Ratio ≤0 25	0 0	0 0	1 4	0 0	0 0	0 7
NUMBER OF EYES	13	23	71	16	15	138

TABLE 6 *Percentage frequency distribution of m_d/a_c (mean area of cup below plane of disc/area of cup on plane of disc) ratio in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

m_d/a_c RATIO	REFRACTION (D) R (—3>Ref)	R_2 (—3≤Ref<±0)	R_3 (±0≤Ref ≤+1)	R (+1<Ref≤+4)	R (Ref>+4)	TOTAL
0≤ Ratio ≤0 05	0 0	0 0	13 6	6 3	0 0	7 6
0 05< Ratio ≤0 1	0 0	4 4	6 0	0 0	0 0	3 8
0 1< Ratio ≤0 15	0 0	13 0	18 2	6 3	20 0	14 3
0 15< Ratio ≤0 2	100 0	82 6	56 0	87 6	80 0	71 4
0.2< Ratio ≤0 25	0 0	0 0	6 1	0 0	0 0	3 0
NUMBER OF EYES	13	23	66	16	15	133

The percentage distribution of the a_c / a_d ratio is shown in Table 10 In the myopic eyes there is no a_c / a_d ratio of 0 2 or below as in the emmetropic and hyperopic eyes In the group R_5 all the a_c / a_d ratios are 0 6 or smaller while in all other groups a_c / a_d ratios between 0 6 and 0 8 can be found The range of values for the a_c / a_d ratio is 0 1 — 0 8 An a_c / a_d ratio of 0 6 or below is found in 72 % of the eyes

TABLE 10 *Percentage frequency distribution of a_c/a_d (area of cup on plane of disc/area of disc) ratio in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

a_c/a_d RATIO	REFRACTION (D)					
	R (−3>R f)	R (−3≤Ref<±0)	R (±0≤R f ≤+1)	R (+1<Ref≤+4)	R (R f>+4)	TOTAL
)≤ Ratio ≤0 1	0 0	0 0	0 0	0 0	0 0	0 0
1< Ratio ≤0 2	0 0	0 0	2.8	6 3	6 7	2 9
2< Ratio ≤0 3	15 4	4 4	1 4	6 3	13 3	5 1
3< Ratio ≤0 4	15 4	17 4	14 1	6 3	13 3	13 8
4< Ratio ≤0 5	23 1	21 7	19 7	25 0	33 3	22.5
5< Ratio ≤0 6	23 1	26 1	31 0	18 8	33 3	29 3
6< Ratio ≤0 7	15 4	26 1	21 1	31 3	0 0	20 3
7< Ratio ≤0 8	7 7	4 4	9 9	6 3	0 0	7 [illegible]
NUMBER OF EYES	13	23	71	16	15	138

TABLE 11 *Percentage frequency distribution of m_d/a_d (mean area of cup below plane of disc/area of disc) ratio in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

m_d/a_d RATIO	REFRACTION (D)					
	R (−3>R f)	R (−3≤Ref<±0)	R (±0≤R f ≤+1)	R (+1<R f≤+4)	R (Ref>+4)	TOTAL
≤ Ratio ≤0 05	15 4	8 7	10 6	12 5	13 3	11 3
)05< Ratio ≤0 1	61 5	65 2	54 6	50 0	86 7	60 2
)1< Ratio <0 15	23 1	26 1	25 8	37 5	0 0	24 0
)15< Ratio ≤0 2	0 0	0 0	3 0	0 0	0 0	1 5
)2< Ratio ≤0 25	0 0	0 0	3 0	0 0	0 0	1 5
)25< Ratio ≤0 3	0 0	0 0	3 0	0 0	0 0	1 5
NUMBER OF EYES	13	23	66	16	15	133

The percentage distribution for the ratio m_d / a_d appears in Table 11 The only group where all the m_d / a_d ratios are 0 1 or below is R_3 The m_d / a_d values are of equal order among the other groups 97 % of the eyes have m_d / a_d ratios of 0 2 or below

Tests of ratio differences

In order to investigate the differences in the characteristic ratios of the cup and disc in different refraction groups the mean values and standard deviations of the characteristic ratios were compared with each other by t test

The mean values and standard deviations of the characteristic ratios and of refraction in the different refraction groups and in the whole sample are shown in Table 12

TABLE 12 *Mean values and standard deviations of variables in refraction groups R_1 R_2 R_3 R_4 R_5 and in the whole sample*

VARIABLE	R_1 mean value	R_1 standard deviation	R_2 mean value	R_2 standard deviation
h_d/h_c	0 62	0 20	0 66	0 16
m_c/a_d	0 13	0 03	0 12	0 03
m_d/a_c	0 17	0 01	0 17	0 02
h_d/v_d	0 75	0 34	0 63	0 22
h_c/v_c	0 79	0 34	0 64	0 19
m_c/a_c	0 28	0 10	0 25	0 09
a_c/a_d	0 50	0 16	0 50	0 13
m_d/a_d	0 08	0 03	0 08	0 03
Ref	—4 8	1 0	—1 5	0 9

VARIABLE	R_3		R_4	
	mean value	standard deviation	mean value	standard deviation
h_d/h_c	0 72	0 19	0 70	0 24
m_c/a_d	0 12	0 03	0 12	0 03
m_d/a_c	0 15	0 07	0 16	0 04
h_d/v_d	1 43	1 18	0 59	0 20
h_c/v_c	1 39	1 09	0 63	0 15
m_c/a_c	0 25	0 09	0 24	0 11
a_c/a_d	0 53	0 14	0 52	0 16
m_d/a_1	0 09	0 06	0 09	0 03
Ref	0 51	0 34	1 6	0 7

VARIABLE	R_5		WHOLE SAMPLE	
	mean value	standard deviation	mean value	standard deviation
h_d/h_c	0 61	0 18	0 69	0 19
m_c/a_d	0 12	0 03	0 12	0 03
m_d/a_c	0 16	0 02	0 16	0 05
h_d/v_d	0 88	0 61	1 05	0 94
h_c/v_c	0 85	0 54	1 04	0 86
m_c/a_c	0 31	0 12	0 26	0 10
a_c/a_d	0 42	0 12	0 51	0 14
m_d/a_d	0 07	0 02	0 09	0 05
Ref	5 9	0 9	0 4	2 6

Tables 13 14 15 and 16 show t values of the mean values calculated for the characteristic ratios in the different refraction groups compared with each other In the tables significant values at the 1 % level are marked with three asterisks at the 5 % level with two asterisks and at 10 % with one asterisk

TABLE 13 *t values of means of characteristic ratios between group R_1 and groups R_2 R_3 R_4 and R_5*

CHARACTERISTIC RATIO	R_1–R_2	R_1–R_3	R_1–R_4	R_1–R_5
h_d/h_c	—0 746	1 76*	—1 02	0 150
m_c/a_d	0 714	—0 520	0 990	0 487
m_d/a_c	0 452	—1 11	0 730	0 825
h_d/v_d	1 27	1 98*	1 50	—0 671
h_c/v_c	1 63	1 89*	1 64	—0 357
m_c/a_c	0 743	—0 756	0 987	—0 751
a_c/a_d	—0 189	0 863	—0 337	1 32
m_d/a_d	0 00495	0 442	—0 184	1 66
DEGREES OF FREEDOM	34	73	26	25

TABLE 14 *t values of means of characteristic ratios between group R_2 and groups R_3 R_4 and R_5.*

CHARACTERISTIC RATIO	R_2–R_3	R_2–R_4	R_2–R_5
h_d/h_c	1 38	—0 639	1 02
m_c/a_d	0 124	0 545	—0 093
m_d/a_c	—1 34	0 531	0 281
h_d/v_d	3 29	0 528	—1 85 *
h_c/v_c	3 32***	0 233	—1 73
m_c/a_c	0 062	0 496	—1 70 *
a_c/a_d	0 893	—0 240	1 90
m_d/a_d	0 621	—0 236	1 92 *
DEGREES OF FREEDOM	85	38	37

TABLE 15 *t values of means of characteristic ratios between group R_3 and groups R_4 and R_5*

CHARACTERISTIC RATIO	R_3 – R_4	R_3 – R_5
h_d/h_c	0 367	2.15
m_c/a_d	0 612	0 0118
m_d/a_c	—0 799	—0 959
h_d/v_d	2 81 •	1 75
h_c/v_c	2 77	1 86
m_c/a_c	0 615	—1 93
a_c/a_d	0 443	2 83
m_d/a_d	0 373	1 40
DEGREES OF FREEDOM	77	76

TABLE 16 *t values of means of characteristic ratios between groups R_4 and R_5*

CHARACTERISTIC RATIO	R_4 – R_5
h_d/h_c	1 27
m_c/a_d	—0 502
m_d/a_c	—0 286
h_d/v_d	—1 79
h_c/v_c	—1 57
m_c/a_c	—1 76
a_c/a_d	—1 78
m_d/a_d	—1 77
DEGREES OF FREEDOM	[illegible]9

From the tables it is evident that group R_5 comprising hyperopic eye with a refraction above +4 0 D is the most distinctive with regard to the characteristic ratios It is best distinguished from the other groups by the a_c/a_d ratio but in respect of the m_c/a_c and m_d/a_d ratios it also diverges to a considerable extent The m_c/a_c ratio distinguishes R_5 from all groups except group R_1 The m_d/a_d ratio distinguishes group R_5 from all other groups apart from groups R_1 and R_3 However the decision risk for the difference of the m_d/a_d ratios in both of these cases does not exceed the value of 20 % In addition it is seen from the tables that group R differs from the other groups with regard to the h_d/v_d and h_c/v_c ratios

Characteristic ratios in right and left eyes

In general the characteristic ratios of the cup and disc approximated closely for both eyes of the same subject The 23 subjects in whom the right and left eyes were studied had a refraction range of ± 0 to +1 0 D

In 80 % of the cases the difference between the h_d/h ratio of the two eyes in the same subject did not exceed 0 3 and in no case did it exceed 0 4 For the m_c/a_d ratios 80 % and 100 % of the subjects showed no differences exceeding 0 04 and 0 052 respectively For the m_d/a_c ratio differences were in 74 % and 100 % of the eyes below 0 08 and 0 18 respectively The h_d/v_d ratio differences were less than 2 0 in 72 % of the cases and less than 3 65 in the total sample Correspondingly the h_c/v_c differences were less than 2 0 for 78 % and less than 3 96 for all the eyes studied Likewise for the m_c/a_c ratio differences did not exceed 0 07 in 70 % of the sample and 0 23 in the total number of eyes 82 % of the a_c/a_d ratio differences were below 0 15 and no single a_c/a_d ratio difference exceeded 0 2 The m_d/a_d differences did not exceed 0 04 in 70 % of the sample and 0 17 in the total number of eyes studied

DISCUSSION

Cup height and cup area

The linear dependence between h_d/h_c ratio and a_c/a_d ratio is positive. This means that both characteristic ratios either increase or decrease simultaneously. In this study the area of the optic disc was used as scale segment. From this it follows that the area of the disc is constant and it may be concluded that there is a positive linear dependence between h_d/h_c and a_c. The results obtained by Pickard (1948), Armaly (1969) and Holm et al. (1972) point in the same direction as the present results. Pickard states that increase in depth tends to take place with enlargement of the cup area but irregularly so. Pickard used the method of drawing the outlines of the cup and disc in their apparent size and noting the depth of the cup in diopters. Armaly states that a large cup/disc diameter ratio is associated with greater cup depth. According to Holm et al. who used photogrammetry in measuring cup volume, a larger cup volume generally correlates with a larger cup/disc diameter ratio.

Cup height and mean cup area

The linear dependence between h_d/h_c ratio and m_c/a_c ratio is negative. This means that when one of the characteristic ratios increases the other decreases. It is known from the positive correlation between the h_d/h_c and a_c/a_d ratios where a_d is constant that the h_d/h_c ratio changes in the same direction as the value of a_c. This means that when the h_d/h_c ratio increases a_c also increases. Because the linear dependence is negative between the h_c/h_c and m_c/a_c ratios the rate of increase of m_c must be less than that of a_c.

The positive linear dependence between the m_c/a_d ratio and the m_d/a_c ratio provides little information since the quantity m_d is subsumed in m_c. The latter fact may cause the significant linear dependency. On the other hand, because we are dealing with surfaces and indeed surfaces of different shapes, the linear dependency is no greater than 0.234.

Characteristic ratios and applanation pressure

In the present study a probably significant positive correlation between a_c/a_d and applanation pressure was found The results are in agreement with those of Armaly and Sayegh (1969) who estimating the cup/disc ratio by ophthalmoscopy found a positive correlation with applanation pressure Long term follow up studies would be necessary to establish whether the correlation between a_c/a_d and applanation pressure is a genetically determined characteristic or whether in these healthy eyes the a_c/a_d ratio is altered by the ocular pressure as is the case in glaucoma

Characteristic ratios and refraction

In the present study no significant correlation was found between the characteristic ratios and refraction The best correlation was found between the a_c/a_d ratio and refraction but it failed to reach a decision risk level of even 10 % Tomlinson and Phillips (1969) found that the cup/disc area ratio showed a significant correlation with refraction whereas the correlation of the cup/disc horizontal diameter ratio with refraction failed to reach a significant correlation at the 5 % level The authors suppose that the cup/disc area ratio is a better index than the cup/disc diameter ratio if the clinical impression is true that the optic disc is vertically oval or at any rate not necessarily round In the present work the areas of the cup and disc were measured but the ratio between them was expressed as a circle diameter ratio

From Fig 4 where the contours of the cup and disc are drawn it is easy to see that it is more accurate to measure the areas of the cup and disc than merely the horizontal diameters The discrepancy between the results obtained in the present study and the results of Tomlinson and Phillips may be explained by the difference in material and methods Tomlinson and Phillips used 75 eyes in their study of these almo 50 % were myopic which differs considerably fr distribution of ametropia in a random sample of the population the results they obtained by marking the border of the cup and photo graphs are more accurate than those obtained g the borders of the cup and disc on ordinary photos th grammetric practice has shown less accurate than stereo techniques proper Moreover it must be in both studies were relatively small Snydacker (1964) of 500 patients observed opthalmoscopically find any

t[h]e size of the cup and refraction a conclusion which is in agreement with the results obtained in the present study

Analysis of characteristic ratio frequency distribution

In the present study the distribution of the characteristic ratios was in most cases unimodal and symmetric and with a few exceptions followed Gaussian statistical distribution Tomlinson and Phillips (1969) in their study based on measurements of cup/disc ratios from stereo photographs found that the cup/disc ratio distribution did not significanly differ from the Gaussian The non Gaussian distribution of the cup/disc ratio found by Snydacker (1964) Hollows and McGuiness (1966) and Armaly (1967) may be explained by the inability of their methods to detect small cups Previous to measurements of the cup volume by Holm et al (1972) no investigations concerning parameters of the optic cup and disc other than the cup/disc ratio (Pickard 1921 1923 1948 Snydacker 1964 Hollows and McGuiness 1966 Witusik 1966 Armaly 1967 1969 Tomlin on and Phillips 1969) have been reported The evolution of previous work on the optic cup/disc ratio is fairly complicated because of the differences in method of examination The most popular methods are direct ophthalmoscopy single photographs of the disc and stereophoto graphy of the disc The two first mentioned are rather inaccurate as is evidenced by the great number of no visible cups reported Ford and Sarwar (1963) in an ophthalmoscopic examination of 6000 subjects noted the absence of cupping in 27 % of them Hollows and McGuiness (1966) in a photographic study measured cup and disc size from single photo graphs by means of a plastic graticule They classified 23 % of all discs as having no visible cup Witusek (1966) who used direct ophthalmoscopy in studying 6500 discs could not find any visible cup in 21 % of the eyes With the method used in the present study a cup could be detected in every eye and the postulation that every disc has a cup however small seems to be verified

In 80 % of the eyes the h_d/h_e ratio was between 0 5 and 1 0 which shows how large a part of the optic cup is below the plane of the disc

The distribution of the h_d/v_d and h_e/v_e ratios is of the same type which partly depends on the fact that h_d and v_d are subsumed in h_e and v_e

The range of values for the a_e/a_d ratio was from 0 1 to 0 8 and in 72 % of the eyes an a_e/a_d ratio of 0 6 or below was found These results are in agreement with the results of Tomlinson and Phillips (1969) who found a

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The range of values for the a_c/a_d ratio was from 0 1 to 0 8 and in 72 % of the eyes an a/a_d ratio of 0 6 or below was found These results are in agreement with the results of Tomlinson and Phillips (1969) who found a

cup/disc diameter ratio below 0 55 in 67 % of the eyes Pickard (1923) stated that the physiologic excavation never exceeds 60 % of the area of the disc in normal cases Snydacker (1964) stated that cup/disc ratios larger than 0 5 are not common whereas in the present study 56 % of the eyes had a cup/disc ratio between 0 5 and 0 8 Armaly (1967) found a cup disc ratio less than 0 2 in 45 % of the cases and a ratio less than 0 3 was found in 67 % The reason for the disagreement between these results and those in the present study may be sought in the different methods used for it is almost impossible to mark the border of the cup exactly on single photographs or to estimate the size of the cup by ophthalmoscopy

In nine eyes the bottom of the cup was situated above the plane of the disc There seems to be no difference between the distribution in the different refraction groups In the present study five of the cups belonged to myopic eyes and four were found in emmetropic and hyperopic eyes

Tests of characteristic ratio differences

It has been a common clinical impression that the cup/disc ratio is greater in myopic eyes However when the means of the a_c/a_d ratios were compared with each other by t test in the different refraction groups group R_1 (—3>Ref) was the only one that did not differ from group R (Ref>+4) at a 10 % decision risk level On the other hand the myopic eyes in the present study showed no small cups with a cup/disc ratio of 0 2 or below as did the emmetropic and hyperopic eyes The conception that *myopic eyes have large cup is perhaps to be explained on this basis*

Comparison between right and left eyes

The finding of the present study that the characteristic ratios approximate closely for both eyes in the same subject is in agreement with the results of previous authors Snydacker (1964) in an ophthalmoscopic and photographic study states that the optic disc is usually the same in each eye of the same subject Armaly (1967) found that in 92 % of the total sample the difference in cup/disc ratios between the two cups did not exceed 0 1 and in 99 % it did not exceed 0 2 Richardson (1968) examining by ophthalmoscopy 483 normal newborn infants fourd marked optic cup asymmetry in only 0 6 %

The similarity of the characteristic ratios in the two eyes of the same subject supports the clinical contention that a *difference between the two* eyes in most of the characteristic ratios is clearer evidence of possible pathology than are the characteristic ratios in themselves

SUMMARY

A new method of applying stereophotogrammetric and computer techniques in measurements of structures in the eye ground is presented. *This method may be used to obtain data on the size and shape of the optic* cup and disc and on changes that may occur in them, thus solving problems that most ophthalmologists meet almost daily.

The equipment and measuring technique for stereophotogrammetry of the optic cup and disc are described in detail. An artificial test eye is described by means of which scale correction coefficients for this equipment applicable for human eye measurements were calculated. Because complete correspondence of the test eye and the human eyes was not possible, the use of relative values was unavoidable and the conclusions drawn in this study are based on ratios of measured values.

The material of 138 eyes of 115 healthy males aged 18—24 years was *divided into five refraction groups. Eyes with a refraction exceeding —3.0* D were placed in group R_1. The rest of the myopic eyes with a refraction of —3.0 D or below were placed in group R_2. Group R_3 consisted of eyes with a refraction ranging from ± 0 to $+1.0$ D and R_4 contained the hyperopes with a refraction of over $+1.0$ D up to $+4.0$ D. Group R_5 comprised eyes with a refraction above $+4.0$ D. In the subjects belonging to group R_5 both eyes were subjected to stereophotogrammetrical examination, but in all the other subjects only the right eye.

The reliability of the method was tested, and on the basis of the study some quantity ratios from the measurements of the optic cup and disc were selected as characteristic ratios. These were as follows:

h_d/h_c = height of cup to plane of disc/height of cup to uppermost closing contour

m_c/a_d = mean area of cup/area of disc

m_d/a_c = mean area of cup below plane of disc/area of cup on plane of disc

h_d/v_d = height of cup to plane of disc/volume of cup below plane of disc

h_c/v_c = height of cup to uppermost closing contour/volume of cup

$m\ /a_c$ = mean area of cup/area of cup on plane of disc

$a\ /a_d$ = area of cup on plane of disc/area of disc

m_d/a_d = mean area of cup below plane of disc/area of disc

The characteristic ratios were used in analysing material in order to study their correlation and variation in the total material and in the different refraction groups In addition the characteristic ratios of the right and left eyes in the subjects belonging to group R_1 were compared with each other

A highly significant positive correlation was found between the h_d/h_e ratio and a_e and a highly significant negative correlation was found *between the h_d/h_e and m_e/a_e ratios A significant positive correlation* between m_e/a_d and m_d/a_e was shown

A probably significant positive correlation between a_e/a_d and applanation pressure was found

No significant correlation was found between the characteristic ratios and refraction

The distribution of the characteristic ratios was in the majority of cases unimodal and symmetric and close to Gaussian statistical distribution

The range of values for the h_d/h_e ratio was from 0 5 to 1 0 in 80 % of the eyes In all the myopic eyes the h_d/h_e ratio was more than 0 3 where as in the emmetropic and hyperopic eyes ratios of 0 3 or below could be found

The distribution of the m_e/a_d ratios was fairly similar The range of values for the m_e/a_d ratio was 0 2 or below in 99 % of the eyes and for the m_d/a_e ratio 0 2 or below in 97 %

A range from 0 to 1 0 was found in 70 % of the h_d/v_d and in 72 % of the h_e/v_e ratios and a range from 1 0 to 5 0 in the remaining 30 % and 28 %

The distribution of the m_e/a_e ratio was almost the same in all refraction groups 89 % of the eyes showed an m_e/a_e ratio from 0 1 to 0 4 and m_e/a_e ratios above 0 7 were not found

The range of values for the a_e/a_d ratio was between 0 1 and 0 8 An a_e/a_d ratio of 0 6 or below was found in 72 % of the eyes In the myopic eyes no a_e/a_d ratio of 0 2 or below was found as in emmetropic and hyperopic eyes In group R_3 all the a_e/a_d ratios were 0 6 or smaller while in the other groups ratios between 0 6 and 0 8 were found

The range of values for the m_d/a_d ratio was in 97 % of the eyes 0 2 or below R_1 was the only group that had no m_d/a_d ratios above 0 1

When the t values of the means calculated for the characteristic ratios in the different refraction groups were compared with each other group R_1 was the most distinctive It was best distinguished from the other groups by the a_e/a_d ratio but also the m_e/a_e and m_d/a_1 ratios served to dist

inguish it In addition group R_3 diverged from the other groups in the h_d/v_d and h_c/v_c ratios

In general the characteristic ratios of the cup and disc were found to approximate closely for both eyes in the same subject Of the various ratios two may serve to reflect this overall similarity In 80 % of the subjects studied the difference in h_d/h_c of right and left eye in the same subjects was 0 3 and in no case did it exceed 0 4 and a_c/a_d ratio differences did not exceed 0 15 in 82 % of the cases or 0 2 in the total cases studied

REFERENCES

Allen L Kirkendall W M Snyder W B & Frazier O (1966) Instant positive photographs and stereograms of ocular fundus fluorescence *Arch Ophthal 75* 192—198

Armaly M F (1967) Genetic determination of cup/disc ratio of the optic nerve *Arch Opthal 78* 35—43

Armaly M F (1969) The correlation between appearance of the optic cup and visual function *Trans Amer Acad Ophthal Otolaryng 73* 898—913

Armaly M F & Sayegh R E (1969) The cup disc ratio The findings of tonometry and tonography in the normal eye *Arch Ophthal 82* 191—196

Bjorn H Lundqvist C & Hjelmstrom P (1954) A photogrammetric method of measuring the volume of facial swellings *J dent Res 33* 295—308

Colenbrander M C (1960) Measurement of the excavation *Ophthalmologica* (Basel) *139* 491—493

Crock G W (1970) Stereotechnology in medicine *Trans ophthal Soc U K 90* 577—636

Crock G W & Parel J M (1969) Stereophotogrammetry of fluorescein angiographs in ocular biometrics *Med J Aust II* 586—590

Ford M & Sarwar M (1963) Features of a clincally normal optic disc *Brit J Ophthal 47* 50—52

Forsius H Eriksson A Nuutila A Vainio Mattila B & Krause U (1969) *A genetic study of three rare retinal disorders dystrophia dysacusis* syndrome x chromosomal retinoschisis and grouped pigments of the retina p 94 In a symposium held at the Johns Hopkins Hospital Baltimore Md May 26—31 1969 *Birth Defects Original Article Series* vol VII No 3 publ March 1971

Halberg G P (1969) Charting and scoring the optic disc *Arch Ophthal 82* 149—150

Hallert B (1964) *Fotogrammetri* p 13 P A Norstedt & Soners Forlag Stockholm

Hollows F C & McGuiness R (1966) The size of the optic cup *Trans ophthal Soc N Z 19* 33—38 (publ 1967)

Holm O C Becker B Asseff C F & Podos S M (1972) Optic disc cup volume *Amer J Ophthal 73* 876—881

Holm O & Krakau C E T (1970) A photographic method for measuring the volume of papillary excavations *Ann Ophthal 1* 327—332

Krakau C E T (1949) A simple apparatus for measuring level differences in the eye ground *Acta ophthal* (Kbh) *27* 263—265

Krakau C E T (1956) Papillary protrusion measurements by means of streophotographs of the fundus *Acta ophthal* (Kbh) *34* 140—145

Laemann O (1950) *Die Photogrammetrie in ihrer Anwendung auf nicht topographischen Gebieten* S Hirzel Verl Leipzig

Mikuni M Maeda H, Fujii S & Togano M (1971) Stereometrische Rekonstruktion und quantitative Messung der Erhabenheit am Augenhintergrund mit Hilfe der Stereophotographie *Klin Mbl Augenheilk 159* 747—754

Parr J C (1966) Clinical estimation of optic disc cupping with description of a graticule *Trans ophthal Soc N Z 17* 93—106

Pickard R (1921) Variations in the size of the physiological cup and their relation to glaucoma *Proc roy Soc Med 14* 31—40

Pickard R (1923) A method of recording disc alterations and a study of the growth of normal and abnormal disc cups *Brit J Ophthal 7* 81—90

Pickard R (1948) The alterations in size of the normal disc cup *Brit J Ophthal 32* 355—361

Richardson K T (1968) Optic cup symmetry in normal newborn infants *Invest Ophthal 7* 137—140

Snydacker D (1964) The normal optic disc Ophthalmoscopic and photographic studies *Amer J Ophthal 58* 958—964

Tomlinson A & Phillips C I (1969) Ratio of optic cup to optic disc in relation to axial length of eyeball and refraction *Brit J Ophthal 53* 765—768

Witusik W (1966) Types of physiological excavation of the optic nerve head *Ophthalmologica* (Basel) *152* 57—67

ACTA OPHTHALMOLOGICA

SUPPLEMENTUM 116

ON THE OSCILLATORY POTENTIALS OF THE HUMAN ELECTRORETINOGRAM IN LIGHT AND DARK ADAPTATION

BY

LILLEMOR WACHTMEISTER

MUNKSGAARD

COPENHAGEN 1972

ACTA OPHTHALMOLOGICA SUPPLEMENTUM 116

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To my parents and Carl-Fredrik and Helena

This survey is based on the following four papers

I Algvere P Wachtmeister L and Westbeck, S On the oscillatory potentials of the human electroretinogram in light and dark adaptation I Thresholds and relation to stimulus intensity on adaptation to short flashes of light A Fourier analysis

II Algvere, P and Wachtmeister L On the oscillatory potentials of the human electroretinogram in light and dark adaptation II Effect of adaptation to background light and subsequent recovery in the dark A Fourier analysis

III Wachtmeister L On the oscillatory potentials of the human electroretinogram in light and dark adaptation III Thresholds and relation to stimulus intensity on adaptation to background light

IV Wachtmeister L On the oscillatory potentials of the human electroretinogram in light and dark adaptation IV Effect of adaptation to short flashes of light Time interval and intensity of conditioning flashes A Fourier analysis

References to these papers will be made by the Roman numerals listed above

Contents

INTRODUCTION 9

HISTORICAL SURVEY 11
I Basis of the oscillatory potentials 11
II Origin of the oscillatory potentials 12
III Process of adaptation 13

AIM OF THE PRESENT STUDIES 16

PAPER I On the oscillatory potentials of the human electroretinogram in light and dark adaptation I Thresholds and relation to stimulus intensity on adaptation to short flashes of light A Fourier analysis 17

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PAPER IV On the oscillatory potentials of the human electroretinogram in light and dark adaptation IV Effect of adaptation to short flashes of light Time interval and intensity of conditioning flashes A Fourier analysis 23

GENERAL DISCUSSION 24
I Range of sensitivity of the oscillatory potentials 24
II Retinal state of adaptation and the oscillatory potentials 25

ACKNOWLEDGEMENT 28

REFERENCES 30

Introduction

The action potential of the retina in response to onset and cessation of light as a cornea positive deflection the electroretinogram (ERG) was first discovered by Holmgren 1865 It was later found to be a biphasic response with a negative potential the a wave followed by a positively directed b wave and a slower positive component the c-wave There was also found an off effect the d wave on cessation of light stimulus This concept has been the subject of many important classical studies some of which are those of Dewar & McKendrick (1872/73) Kuhne & Steiner (1880) Gotch (1903) Einthoven & Jolly (1908) Granit (1933 1947) Karpe (1945)

The classical a b, c and d waves of the ERG have been considered as an electric expression for different processes of the retina in response to a light stimulus (Granit 1933 1947) The a and b waves of the ERG have been analysed by Brown (1968) and found to be an algebraic summation of three different components *viz* the negative late receptor potential (LRP) the positive d c component and the positive b wave

Recently a negative dc response originating in the inner nuclear layer of the retina has also been suggested on the basis of a component analysis of the sheep s ERG (Knave Møller & Persson 1972) A re appraisal of the components has also been made by Rodieck (1972) the essential modification being an enlargement of the slower potentials

In addition to the ortodox a- b c- and d waves the polyphasic mass response there have been found more complicated components as two rapid components, which make up the early receptor potential (ERP) (Brown & Murakami 1964 Yonemura Kawasaki & Hasvi 1966) and precede the a wave (the late receptor potential LRP) a proximal negative response (PNR) (Burchardt 1970) fast retinal potentials (FRP) (Dawson & Stuart 1968) and minor waves (wavelets) or oscillatory potentials (Noell 1951 Cobb & Morton 1953 Heck & Rendahl 1957 and many others)

The dual nature of the potential changes of the retina assigned to the duplicity of the retinal organization into a rod and cone system, has also been demonstrated (Granit & Munsterhjelm 1937 Motokawa & Mita 1942 Adrian 1944 1945 and many others) The b wave was resolved into two peaks a fast positive deflection the x-wave or photopic b wave and a slower scotopic b wave They were found to be correlated to the photopic and scotopic luminosity function of the retina respectively (Riggs Berry & Wayner 1949 Johnson Riggs & Schick 1966)

Thus, the ERG is a retinal response to light stimulation and represents a summation of mechanisms of different latencies, different sensitivities to light and different rates of recovery from preceding illumination

Historical survey

I *Basis of the oscillatory potentials*

A contour of oscillations on the ascending phase of the b wave was first presented by Granit & Munsterhjelm (1937) on the records of the ERG of the frog and by Noell (1951) in the pigeon turtle and rabbit Numerous later studies have been performed on several animal species and particularly large wavelets were recorded in cone dominated retinas (Armington 1954 Crescitelli 1961 Granda 1962 Yonemura 1962 Yonemura & Hatta 1962 Yonemura Masuda & Hatta 1963 Nye 1968 and many others)

The first report on oscillatory potentials in the human ERG is the one by Cobb & Morton 1953 They noticed in response to short high intensity flashes four to six smaller waves superimposed on the b wave of the ERG

Ronchi & Grazi (1956), as well as Bornschein & Goodman (1957), also demonstrated in response to a light stimulus of rapid rate of rise these subwaves of the human ERG Bornschein & Goodman (1957) first suggested that the oscillatory peaks represented phases of a regular oscillatory response behaving independent of the a and b wave

In response to a slowly flickering light of moderate intensity distinct oscillatory potentials were elicited (Heck & Rendahl 1957 Rendahl 1958) They additionally claimed the third and fourth peak to be variously affected by chromatic adaptation in protanopia and deuteranopia Other authors failed to identify any specific colour mechanisms as the basis for the individual oscillatory potentials (Armington 1954 Granda 1962 Nye 1968) or the fast retinal response (FRP) related to the oscillatory potentials (Adams & Dawson 1971)

The maximal chromatic sensitivity of the oscillatory potentials was demonstrated to be at the red end of the spectrum (Rouher Sole & Alfieri 1966) On the other hand Adams & Dawson (1971) also found a relative increase in sensitivity of the fast retinal potentials (FRP) in response to short wavelengths of the spectrum under mesopic adaptation

Most prominent oscillatory potentials were distinguished in cone dominated eyes, *i e* the pigeons retina (Yonemura Masuda & Hatta 1963) They were absent in achromatopsia and reduced in protanopia (Jacobson Hirose & Popkin 1965) A selective reduction of the oscillatory potentials was observed in diabetic retinopathy (Yonemura 1962 Simonsen 1965) in some circulatory disorders and other pathological conditions such as uveitis retinal detachment siderosis (Aoki 1960 Yonemura 1962, Nagata 1962 Noell & Ruedemann

1966, Perdriel Soussen Desbordes & Leblanc 1964, Stangos, Rey Meyer & Thorens 1972, and others) The oscillatory peak latency was found to decrease as stimulus intensity was raised (Armington 1954, Bornschein & Goodman 1957, Buckser 1968, Samson Dollfus 1969, Brunette 1972) Some authors (Cobb & Morton 1953, Yonemura 1962, Jacobson & Masuda 1966, Auerbach 1967, Tsuchida, Kawasaki & Jacobson 1971) reported that when using different intensities of stimulus the frequency of the oscillatory peaks remains essentially unaltered *i e* at intervals of approximately 7 msec (frequency about 140 Hz) Other workers (Genest 1964, Algvere 1967, Nye 1968) observed the oscillations to be spaced at irregular intervals

II *Origin of the oscillatory potentials*

The origin of the oscillatory potentials has been the subject of many hypotheses The nature of the oscillations is still obscure

Granit (1947 1962) claimed the oscillatory peaks to be an average result of many processes of different size, different rate of appearance and different rise Buckser (1968) proposed the multipeaked b waves of the ERG of rat and frog to reflect the summation of several b waves of different peak time not excluding a possible influence by the b wave An antidromic stimulation of optic nerve fibers of cat did not induce the oscillatory rhythm (Doty & Kimura 1963) The oscillations are not primarly initiated by the ganglion cells nor do centrifugal fibers of the optic nerve affect the generation of the wavelets of the ERG (Yonemura & Tsuchida 1969 Winkler 1972)

Animal studies with the aid of intraretinal and intracellular recordings with microelectrodes combined with electron microscopy studies further elucidated the origin of the oscillatory potentials (Tomita & Funaishi 1952 Brindley 1956 Yonemura Masuda & Hatta 1963 Yonemura & Hatta 1966 Brown 1968 Burckardt 1970 Dowling 1970 Werblin 1970 1971 and others) Brindley (1956) localized the oscillations to the tangentially oriented structures of the inner nuclear layer of frog retina Brown (1968) postulated that the oscillatory potentials are generated in neural feed back circuits in the inner nuclear layer as studied in the cynomolgus monkey On morphological basis a feed back synaptic arrangement of amacrines and bipolars was suggested by Dowling (1970) and Werblin (1970 1971) Such arrangement would serve very well as a gain control or adaptation mechanism When retina was light-adapted the width of the centre of bipolar receptive field was not changed but the surround antagonism became more apparent Most of the adaptive processes appeared to be completed at bipolar cell level before they were carried through to amacrine ganglion cell level (Werblin 1971)

III *Process of adaptation*

The human eye is able to adapt and function over an enormous span of light intensities, discriminating over a luminance range of about 10 billion to 1 (Rushton 1965 a)

Hecht s classical photochemical theory (Hecht 1920) that changes in the sensitivity of the visual systems are related to the bleaching and regeneration of visual pigments has been modified Non photochemical (neural) factors (Rushton & Westheimer 1962 Dowling 1963) and intermediate products of bleaching as metarhodopsin which seem to have a desensitizing effect on retina (Donner & Reuter 1967) also contribute to visual adaptation

Granit Munsterhjelm & Zewi (1939) obtained the first experimental evi dence of the fact that the amount of photopigment present is insufficient to account for the change of the amplitude of the ERG

Craik & Vernon (1941) demonstrated that visual adaptation is retinal in origin by showing that adaptation proceeds normally in a human subject even if the eye is temporally blinded by pressure on the eye ball during the period of light adaptation The b wave of the human ERG has adaptation properties comparable to those observed in psychophysical adaptation (Karpe & Tansley 1948 Johnson 1949 Johnson & Riggs 1951 Best & Bohnen 1956) The site of adaptation in the visual system is more peripheral than the gang-lion cells

Brown & Watanabe (1965) noticed that the a wave of the local ERG of monkey does not show so much adaptation to short flashes of lights as did the b wave Lipetz (1961 1962) studying the frog retina suggested that the mechanisms subserving adaptation are located more centrally than the receptor outer segments

Rushton (1972) proposed on the basis of psychophysical experiments two mechanisms of adaptation a desensitization, presumably occurring distal to the horisontal cells — in the receptors themselves and ii) a scaling down of retinal signals proximal to the receptors probably by the horisontal cells and their connections

Dowling & Ripps (1971) consider part of the non photochemical adapta tion to take place in the receptor cells Frank (1971) suggested the neural phase to be mediated by a mechanism of passive ionic diffusion

Adaptation to light Numerous experiments on human subjects with psycho-physical techniques for estimation of threshold have shown that most of the change in light adaptation is completed within 0 1 second although it takes several seconds for the threshold to settle to its final value (Crawford 1947, Baker 1955 1963 and many others) Auerbach (1967) noticed a discrepancy by a factor of at least 100 between the relative changes in the amplitude of the ERG and the visual pigment concentration on transition from darkness to

light The main process of adaptation to light is very fast, requiring only the time needed for a neural (or synaptic) event to occur, unrelated to the amount of bleaching of visual pigment

van Lith (1966) observed that the elevation of threshold (psychophysical or electrical response) depends almost entirely on the intensities of the background or adapting light, although the required stimulus intensity is about 10^{3} times (for a criterion of 35 mV-electrical response) that for the absolute sensory threshold At high adapting intensities that substantially bleached photopigments the incremental threshold was raised at about the same rate as it did with lower unbleaching intensities (Dowling 1963, 1967, van Lith 1966) The change in log visual threshold (sensory or electrical) was approximately linearly correlated to rhodopsin concentration of retina (Dowling & Wald 1958 Rushton 1961 b)

Purkinje shift Since Purkinje s personal observation (1825) it is known that the sensitivity of the dark-adapted human eye is greatest in the blue region of the spectrum but changes to the yellow region when light adapted Later numerous studies have shown the human dark adapted (scotopic) visibility (luminous efficiency) curve to have a maximum at approximately 510 nm and quantitatively to correspond to light absorption curve of visual purple (Konig 1894 Wald 1945, Crawford 1949 and many others) A change of the photopic luminous efficiency curve for the light adapted eye to about 560 nm was demonstrated by Walters & Wright 1943 Wald 1945 and many others Psychophysical investigations (Walters & Wright 1943, Le Grand 1968) showed that the scotopic luminosity curve holds below a background luminance of 10^{-3} cd/m^{2} and above that luminance the Purkinje shift should occur van Lith (1966) was able to demonstrate that the maximal spectral sensitivity of the human eye changed from short wavelengths (blue) to long wavelengths (yellow) at a background luminance of about 10^{-} cd/m

Adaptation to darkness The adaptation to darkness is more complicated When studied in the adaptometer two phases of recovery of sensitivity can be distinguished The first phase is related to the adaptation of the cones Separated from it by the Kohlrausch kink (Kohlrausch 1922 1931) the second phase shows the adaptation of the rods

The human sensory dark adaptation curves were observed to differ in shape when the strength and duration of the adapting light varied (Blanchard 1918, Hecht Haig & Chase 1937 and many others)

After preexposure to dim adapting intensities which do not bleach any measurable amount of visual pigments the recovery of the retinal sensitivity is extremely rapid and comparable with the rapid loss of sensitivity during light adaptation With bright adapting intensities which bleach visual pigments, a slow phase of dark adaptation is observed

Dowling (1963) studying the rat s retina and Rushton (1965 a 1972) study

ing human subjects also recognized these two types of adaptation and identified them as the rapid neural phase and the slow photochemical phase of adaptation

Rushton (1961 b 1963 1965 b) combined psychophysical and retinal densitometric measurements on the human eye and found a relation between log threshold and pigment concentration of the rods and the cones after an exposure to bright light which bleached most of the visual pigments The time constant of cone pigment regeneration was demonstrated to be more rapid (about 130 seconds) than that of the rod pigment (about 7 minutes) (Campbell & Rushton 1955 Rushton 1963 1965 b) Rushton (1961 a) also showed that the rods did not start to function until over 90 % of their rhodopsin had been regenerated *The second branch of the adaptometric curve indicating the threshold of the rods* was shown to be displaced later in time after bright light adaptation than after dim pre illumination The shape of the branch was also changed The sensitivity of the rods increased much slower after intense pre illumination

After a long exposure to very strong light the visual cells show degenerative changes and there is a reduction in the amplitude of the electroretinographic response (Noell Walker Kang & Berman 1966 Gorn & Kuwabara 1967 Knave 1970)

Aim of the present studies

The aim of the present studies was to analyse the oscillatory potentials of the human ERG in light and dark adaptation My intention was to give a certain contribution to the present knowledge of the complicated function of adaptation of the human eye as reflected in the behaviour of the oscillatory potentials

The human ERG was regarded as consisting of a biphasic slow response (a and b-waves) with superimposed oscillations By means of a mathematical estimation (a combined impulse response and Fourier analysis) the oscillatory potentials were isolated from the total ERG and the dominating frequency and total energy attributable to the oscillations were calculated

In dark-adapted eyes the large oscillations are known to vanish To study the oscillatory potentials three consecutive flashes were given and ERG studied in response to the third (stimulus) flash Using this created steady state of adaptation a study of the thresholds and relation to stimulus intensity in dark adaptation was made (I) Oscillatory potentials elicited in dark adaptation were studied on adaptation to background light their subsequent recovery in the dark was followed and a comparison with the a- and b waves was made (II) The change in thresholds (incremental thresholds) and the stimulus response curve of the oscill tory response and the a and b waves were then described (III) Finally the importance of the time interval and intensity of the first two (conditioning) flashes for the state of light adaptation induced to elicit the oscillatory potentials was analysed (IV)

Thresholds and relation to stimulus intensity on adaptation to short flashes of light A Fourier analysis

To study the oscillatory potentials of the human ERG in dark adaptation a series of three short flashes of light were given at a constant interval of 30 seconds This created a steady state of retinal adaptation The first two flashes in each series were referred to as conditioning flashes Maximum intensity of the flash was about 5×10^4 photopic cd/m This performance enabled a study of the thresholds and the relation to stimulus intensity of the oscillatory potentials which in complete dark adaptation are known to vanish (Algvere 1968 DeMolfetta Spinelli & Polenghi 1968)

The apparatus for recording the oscillatory potentials was essentially the same as that described by Algvere & Westbeck (1972) The light stimulus was delivered by an electronic flash mounted in a lamphousing specially constructed for ERG (Karpe & Algvere 1967)

To measure the energy and dominant frequency of the oscillatory potentials the ERG was regarded as consisting of a biphasic slow response (a and b wave) with superimposed oscillations The ERG curve was digitized and the oscillatory potentials of the total ERG were isolated by the use of an impulse response analysing program expressed in the programming language Algol and adapted to the computer IBM 360 (Westbeck 1972 Algvere & Westbeck 1972) The energy and dominant frequency attributable to the oscillatory response was illustrated in the energy density spectrum These calculations permitted a detailed analysis of the isolated oscillatory potentials as there would otherwise be an interference between the a and b waves and the oscillatory potentials

Irrespective of the intensity of the conditioning flashes which were of constant intensity or successively increasing with the intensity of the third (stimulus) flash in each series the oscillatory potentials were recorded (by a corneal electrode) at approximately the same stimulus intensity as the a wave and at somewhat stronger intensity than that of the photopic b wave The scotopic b wave was elicited in response to a stimulus light of 2—4 log units weaker than the stimulus necessary to evoke the photopic b wave at threshold

There was a linear increase of the energy of the oscillatory potentials on

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In dark adapted eyes the large oscillations are known to vanish. To study the oscillatory potentials three consecutive flashes were given and ERG studied in response to the third (stimulus) flash. Using this created steady state of adaptation a study of the thresholds and relation to stimulus intensity in dark adaptation was made (I). Oscillatory potentials elicited in dark adaptation were studied on adaptation to background light, their subsequent recovery in the dark was followed and a comparison with the a- and b-waves was made (II). The change in thresholds (incremental thresholds) and the stimulus response curve of the oscillatory response and the a- and b-waves were then described (III). Finally the importance of the time interval and intensity of the first two (conditioning) flashes for the state of light adaptation induced to elicit the oscillatory potentials was analysed (IV).

Effect of adaptation to background light and subsequent recovery in the dark A Fourier analysis

The behaviour of the a wave (a photoreceptor potential) on adaptation to a background light and its subsequent recovery in the dark is known to differ from that of the b wave (a potential from the inner retinal layer) (Brown & Watanabe 1965 Cone & Ebrey 1965 Maffei & Poppele 1966 Dowling 1967 Elenius 1967 Frank 1971) The local b-wave of the intraretinal ERG was considerably reduced in amplitude while the reduction of the a wave was insignificant on adaptation to repetitive stimuli of short duration (Brown & Watanabe 1965) The b wave recovery was slow whereas the a-wave rapidly adapted to darkness (Maffei & Poppele 1966 Elenius 1967)

No data on the energy and frequency of the oscillatory potentials of the human ERG on adaptation to backgrounds of various intensities and during the subsequent recovery in darkness could be obtained from the current literature

To enable adaptation to an illuminated background a tungsten filament lamp was used The maximum luminance of the background was about 1 5 $\times$ 10- photopic cd/m corresponding to about 4 1 $\times$ 10- scotopic cd/m

The ERG was recorded after at least 30 minutes of dark adaptation in response to flashes which induced a comparatively strong light adaptation (30 second interval) or a weak light adaptation (3 minute interval) The effect of adaptation to background illumination of different intensities with subsequent recovery in the dark was studied Repetitive flashes delivered every 30 seconds in dark adaptation evoked a much larger oscillatory response than flashes given at 3 minute interval

Oscillatory potentials recorded in dark adaptation at long intervals had a low amplitude and high frequency Adaptation to weak background light which corresponded to the level at which cones begin to function (cone threshold) and which did not bleach any significant fraction of visual pigments facilitated the regeneration of the oscillatory potentials and induced a de crease in dominant frequency During adaptation to darkness the reverse change in energy and frequency occurred

At the level of that background luminance at which the maximal spectral sensitivity of the b wave of the human ERG is known to change from a scoto-

pic to a photopic luminosity curve (van Lith 1966), the energy of the oscilla tory response declined markedly There was no distinct change in energy nor in frequency when passing the rod saturation (Aguilar & Stiles 1954, Rushton 1961 b)

There were different rates of recovery in the dark of the three components of the ERG The a wave recovered rapidly and the b wave slowly The oscilla tory potentials increased during the first 3 minutes in the dark and thereafter declined (when recorded at long intervals) or gained in energy during the 5—6 minutes in the dark (when recorded at short intervals)

The results imply the oscillatory potentials definitely to be related to the photopic retinal function, but some influence from the scotopic system cannot be ruled out Some input from the rod system into the regeneration of the oscillatory potentials might occur This is also supported by the report by Adams & Dawson (1971) on the spectral sensitivity of the fast retinal poten tials (FRP) in mesopic conditions

Thresholds and relation to stimulus intensity on adaptation to background light

The electrical and sensory threshold of the human eye were shown to differ by a factor of 100 (van Lith 1966) Brighter stimulus was required for a criterion voltage of 35 μV (x- and b-wave) for the ERG than that for the visual sensory threshold At about a range of 3 log units above the absolute psychophysical threshold the electrical threshold remained constant Above this range the function of log incremental threshold vs log background light intensity rose according to Weber s law with a slope of the line being 1 0 The corresponding part of the threshold curve of the a wave of the ERG showed a slope of the line close to 0 6 (Biersdorf Granda & Lawson 1966) No systemic study of the range of sensitivity (reciprocity of incremental threshold) of the oscillatory potentials on adaptation to varying steady background light seems to have been published in the current literature

The ERG was studied in response to light stimuli varying over a range of 7 log units of intensity The stimulation interval was kept constant (30 seconds) and the eye adapted to backgrounds of different luminances (varied over a range of 5 log units)

The sensitivity of the b wave changed over a wide range (4 log units) whereas the sensitivity of the a wave and the oscillatory potentials varied only over a range of 1 log unit on adaptation to backgrounds used in this study

The threshold of the oscillatory potentials and the a wave remained low when rod sensation predominated The threshold of the oscillations and the a wave rose when sensitivity of the cones was higher than that of the rods and when only the cone response was apparent (rod saturation) (Aguilar & Stiles 1954 Mandelbaum & Nelson 1960 van Lith 1966 Biersdorf Granda & Lawson 1966) The oscillatory response was most easily elicited when the retina was organized in a pattern where the rods still functioned and the cone response also was evoked

There was a similarity between the incremental threshold curves of the a wave and the oscillatory potentials This was interpreted so that the regeneration of the oscillatory potentials is initiated by the activity of the a wave No sign of rapid decrease in sensitivity *i e* saturation of the response was observed

The stimulus response curve of the oscillations was linear in dim background illumination but changed to a plateau at the level of light adaptation at which the Purkinje shift of the b wave ocurred (van Lith 1966) Dominating photopic activity did not seem to be able to grade the oscillatory response

The slow potentials acted independently of the oscillatory potentials in response to stimulus of different intensities This supported the view first suggested by Bornschein & Goodman (1957) that the origin of the oscillatory potentials is quite separate from that of the a and b wave

Effect of adaptation to short flashes of light Time interval and intensity of conditioning flashes A Fourier analysis

It is known from studies of the local ERG on monkeys (Macaca iris) that the amplitude of the b-waves reduced faster and more than the amplitude of the receptor potential in response to series of stimuli serving both to evoke the electrical response and to light-adapt the retina (Brown & Watanabe 1965) The process of recovery of the rod function of the human retina from suppression indicates an exponential recovery both for the a and b wave as well as for the total ERG (Elenius 1969) Little is known from current literature on the behaviour of the oscillatory potentials in this respect The oscillatory response was therefore analysed (using the same stimulation principle as in previous papers) in response to the third (stimulus) flash in a series of three The interval between flashes was changed and the intensity of the first two (conditioning) flashes varied The sensory threshold of retinal sensitivity measured in a Goldmann Weekers adaptometer was also recorded

The oscillatory potentials were more easily elicited when a certain adaptation to light by previous conditioning flashes was prevailing — *e g* when a short interval between flashes was used or when conditioning flashes were of rather strong intensity The flashes which induced a certain state of light adaptation bleached a neglible amount of visual pigments and the light adaptation induced was explained mainly on account of a neural process (Rushton & Baker 1963 Ripps & Weale 1969)

Using low intensity conditioning flashes or long intervals between flashes the oscillatory response to the third (stimulus) flash was of low energy and high frequency At the time the stimulus flash was delivered the visual threshold was determined by the rod mechanism After strong repetitive light stimulation using shorter intervals and more intense conditioning flashes when the retina was supposed to be organized in a photopic pattern (*cf* Barlow Fitzhugh & Kuffler 1957) there was an increment of energy and a decline in frequency of the oscillatory potentials The oscillatory potentials showed a maximal amplitude in the mesopic range of the dark adaptation curve and seemed to reflect photopic as well as scotopic activity

General discussion

1 *Range of sensitivity of the oscillatory potentials*

The aim of the present studies was to analyse the oscillatory potentials and contribute to the understanding of the complex function of adaptation of the human eye

There is an interference between the oscillations and the slower potentials (a- and b waves) — the rate of rise of the latter may influence the shape and size of the former Therefore the oscillatory response was isolated from the ERG-curve by a mathematical estimation performing a combined impulse response and Fourier analysis This enabled a more advantageous comparison between the oscillatory potentials and the slow potentials (a and b wave) of the ERG response

The results show that the precise configuration of the oscillatory response varies considerably with the recording conditions Important variables include degree of light adaptation (background illumination intensity stimulating interval intensity of conditioning flashes stage of recovery in the dark) and intensity of stimulus

To induce a steady state of retinal adaptation a series of three flashes were given at constant intervals This enabled a study of the thresholds and stimulus intensity ranges of the ERG response both in the dark and during adaptation to a steady background light

It is apparent from the records obtained in dark adaptation that traces of oscillations were recorded at approximately the same intensity as the a wave This is somewhat stronger intensity than that necessary to evoke the photopic b wave The energy of the oscillatory potentials increased over a range of at least three log units of stimulus intensity These increments were independent *of the retinal adaptation caused by previous flashes The linear stimulus* response curve of the oscillatory potentials was evidently similar to that of the a wave of the ERG but was different from that of the b wave which reached a maximum beyond which it was depressed

On adaptation to various background intensities the incremental threshold *curve rose linearly above that adaptation intensity* at which the Purkinje shift of the b wave was supposed to occurr The sensitivity (reciprocity of incremental threshold) of the oscillatory potentials declined above that background intensity at which the sensitivity of the cones is higher than that of the rods This suggests a dual nature of the oscillatory potentials which probably is the *result of photopic* as well as scotopic retinal activity

There was also a resemblance between the incremental threshold curves of the oscillatory potentials and the a wave whereas these two curves differed from that of the b wave The thresholds and stimulus response curves of the *oscillatory response and the a wave in dark adaptation were also similar* These facts evidently show the close relationship between the sensitivity of the oscillations and that of the a wave but that the oscillatory potentials did not appear to be related to the b wave This indicates the oscillations to be related to a process which is initiated by the a wave (late receptor potential) as was suggested Brunette (1972)

The present studies did not suggest a photochemical basis for the change in sensitivity or range of graded response of the oscillatory potentials This occurred at a background illumination bleaching a neglible amount of photo pigments (Rushton 1958/1959 1963 1965 b 1966) These events seem mainly *to be mediated by neural processes* This suggests an intimate connection between the generation of the oscillatory potentials and the organization of retinal pathways The shift between scotopic and photopic pattern seemed to be a state when the sensitivity of the oscillatory response is high

It was further evident that the dominant frequency of the oscillatory potentials recorded at threshold was high and decreased as the stimulus intensity increased This was valid in darkness as well as in light adaptation and when adaptation by previous conditioning flashes *successively* increased with the intensity of the third (stimulus) flash On the other hand if light adaptation by previous (conditioning) flashes was high and constant there was *no change of the low dominant frequency*

II *Retinal state of adaptation and the oscillatory potentials*

In the present investigations the oscillatory potentials were also studied on *adaptation to short flashes of light on adaptation to background light and* during subsequent dark adaptation

The retinal adaptation was of great importance for the appearance of the oscillatory potentials — *regarding the shape energy and frequency*

Photopic sensitivity is recorded during the first part of the dark adaptation curve, although some scotopic function in the human ERG of both a and b-wave has been demonstrated (Granda & Biersdorf 1966) The brightest adapting light used in the present studies bleached about 60 % of the cone pigments (chlorolabe erythrolabe) and about 30 % of the rhodopsin An electric response primarily photopic in nature remained Rod activity at photopic levels of illumination *cannot entirely be ruled out and an interaction presumably* at ganglion cell level seem still to occur under these conditions (Le

Rushton W A H & Westheimer G (1962) The effect upon the rod threshold of bleaching neighbouring rods *J Physiol 164* 318—329
Rushton W A H (1963) Cone pigment kinetics in the protanope *J Physiol 168* 374—388
Rushton W A H (1965 a) The Ferrier Lecture *Proc Roy Soc London Ser B 162* 20—46
Rushton W A H (1965 b) Cone pigment kinetics in the deuteranope *J Physiol 176* 38—45
Rushton W A H (1972) Light and dark adaptation *Vision Res 11* 503—517
Samson Dollfus D (1969) Variations physiologiques de l ERG humain en fonction de l energie lumineuse et de la longeur d ond *Vision Res 9* 357—364
Samson Dollfus D Planiol T & Malandrin C (1964) Electrorétinogramme et ondes e *Bull Soc Opht France 77* 42—46
Simonsen S E (1965) Electroretinographic study of diabetics Preliminary report *Act Ophth 43* 841—843
Stangos N Rey P., Meyer J J & Thorens B (1972) Averaged ERG responses in normal human subjects and ophthalmological patients In Wirth Ed *Symposium on electroretinography* Pacini Pisa p 278—304
Tomita T & Funaishi A (1952) Studies on intraretinal action potential with low resistence microelectrode *J Neurophysiol 15* 75—84
Wald G (1945) Human vision and the spectrum *Science 101* 653—658
Walters J *(1971) Scotopic vision at photopic levels? Vision Res 11 787—798*
Yonemura D (1962) The oscillatory potentials of the electroretinogram *Acta Soc Ophth Jap 66* 1566—1684
Yonemura D & Hatta M (1962) Studies on the electroretinogram of frog tortoise and lamprey *Acta Soc Ophth Jap 66* 355—357
Yonemura D & Hatta M (1966) Studies of the minor components of the frog s electroretinogram *Jap J Physiol 16* 11—22
Yonemura D Kawasaki K & Hasui I (1966) The early receptor potential in the human ERG *Acta Soc Ophth Jap 70* 766—768 Cited in Brown K T (1968) Vision Res 8 633—677
Yonemura D Masuda Y & Hatta M (1963) The oscillatory potentials in the electroretinogram *Jap J Physiol 13* 129—137
Yonemura D & Tsuchida Y (1969) Is the oscillatory potentials in the ERG responsible for the activity of the optic nerve *Acta Soc Ophth Jap 73* 719—723



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SUPPLEMENTUM 118

STUDIES ON THE VASCULATURE AND MYELINATED NERVES OF THE PIG IRIS

by

MATTI SAARI

MUNKSGAARD
COPENHAGEN 1972

STUDIES ON THE VASCULATURE AND MYELINATED NERVES OF THE PIG IRIS

To my mother

ACTA OPHTHALMOLOGICA
SUPPLEMENTUM 118

FROM THE DEPARTMENT OF OPHTHALMOLOGY UNIVERSITY
OF HELSINKI
(HEAD PROFESSOR SALME VANNAS M D)
HELSINKI FINLAND

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This review is based on the investigations published earlier in the following papers to which reference is made in the text using the Roman numerals I–VI

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IV Saari M (1971) Myelinated nerves of the pig iris *Acta ophthal.* (Kbh) *49* 921–937

V Saari M (1972) Vasculature of the pig iris *Ann. Med exp Fenn. 50* 1–11

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CONTENTS

INTRODUCTION 9

REVIEW OF THE LITERATURE 10

OBJECT OF THE INVESTIGATION 12

MATERIAL AND METHODS 13

- Material 13
- Methods 13
  - Macroscopical examination 13
  - Flat preparation method 13
  - Trypsin digestion and bleaching 14
  - Thinned flat preparation 14
  - Injection digest bleaching method 14
  - Serial sections 15
  - Electron microscopy 15

RESULTS AND COMMENTS 16

- Flat mount technique for studying blood vessels and myelinated nerves of the pig iris 16
- Vasculature of the pig iris 18
  - Gross vasculature supplying the pig iris 18
  - Minute vasculature of the pig iris 19
  - Ultrastructure of the microcirculatory bed of the pig iris 21
- Myelinated nerves of the pig iris 24

GENERAL DISCUSSION 26

- Functional significance of the iris vascular patterns 26
- Myelinated nerves of the iris 28

CONCLUDING REMARKS 29

REFERENCES 31

INTRODUCTION

Because of the laminar structure of the eye flat preparations afford an unusually favourable opportunity to study such structures as retinal and choroidal vessels Valuable information on the retinal vessels was obtained with flat preparations (Friedenwald 1949 Ashton 1949) with trypsin digestion technique (Kuwabara & Cogan 1960) and with the injection-digest method (Knight 1966) Fluorescein angiographic findings for the iris in different eye diseases (A Vannas 1969 S Vannas et al 1969 Raitta & S Vannas 1969 Karjalainen 1971) stimulated increasing interest in the iris vasculature at the Helsinki University Eye Hospital Because of this study of the blood vessels of the iris with flat preparations was started in 1969 Being of nearly the same size as the human eye the pig eye was chosen for subject of study and could be used as a model for the human eye This type of material was readily available and the pig iris with its strongly developed vascular wall structures was also assumed to be especially informative

It was important to verify the myelinated nerves seen in flat preparations (I) so as to differentiate them without any doubt from the iris vessels Thus an examination of the course and structure of these nerves was made and included in this study The results obtained in flat preparations for blood vessels and myelinated nerves were confirmed with light microscopical serial sections and electron microscopically

REVIEW OF THE LITERATURE

Vascular architecture of the pig iris

The pig iris is thick and contains a large number of chromatophores (Prince et al 1960) For this reason no accurate picture of the vasculature of the pig iris has been obtained to date in the absence of the requisite special methods H Rohen (1951) found a superficial capillary network in the pig iris and the major arterial circle in its ciliary part

Structure of the iris vessels

Contradictory findings have been reported concerning the media of the iris arterioles Eisler (1930) and Purtscher (1963) described a closed media in he larger arteries of the iris Ikui et al (1960) observed no muscle cells in the iris arteries Hogan et al (1971) state that upon entering the iris the arteries lose a layer of smooth muscle cells and the remaining muscle layer is oriented longitudinally

In addition to endothelial cells the capillaries and venules of the iris show pericytes (Purtscher 1963) On the contrary Hogan et al (1971) reported only endotnelial cells in the iris capillaries and venules

The vessels of the iris have a thick sheath (Arnold 1863) of connective tissue fibres (Gutmann 1903 Purtscher 1963) or a thick adventitia (Fuchs 1885 Leber 1903 Eisler 1930 Wolff 1948 Gregersen 1959 Ikui et al 1960 Duke–Elder & Wybar 1961 Hogan et al 1971) With Mallory s connective tissue stain two tubes, one within the other can be discerned in the vessels of the iris (Wolff 1948 Gregersen 1959) A tubular tissue space is seen between the outer tube and the inner tube or the blood channel proper (Gregersen 1959) The outer tube is the adventitia proper which is continuous with the iris stroma and is really part of it (Wolff) Purtscher (1963) discerned in the vessels of the iris a delicate adventitia weakly attached to the vascular sheath formed by stroma

The ultrastructure of the iris vessels was first described by Tousimis and Fine (1959) in their study of the iris of the rhesus monkey and man They found in these vessels a single layer of endothelial cells It was later confirmed that the vessels of the iris showed a basement membrane and pericytes in addition to endothelial cells (Ikui et al 1960 Tomita 1960 Purtscher 1966 Cunha–Vaz et al 1966) Ikui et al (1960) denied the presence of smooth muscle cells in the iris arterioles Lai (1967) and Vegge and Ringvold (1969) reported smooth muscle cells in the arterioles of the iris but they expressed some doubt in their documentation of these cells Hogan et al (1971) considered that capillaries and venules consisted of endothelial cells alone They described longitudinal muscle cells in the arteries and scattered muscle cells in the veins

As far it is known the structure and ultrastructure of the blood vessels of the pig iris has not been previously described

Innervation of the iris

The first detailed report of the innervation of the iris was presented by Arnold (1863) who described the nerves of the albino rabbit and human iris and since then the innervation of the iris has been widely studied (for references see IV) Observations on the innervation of pig iris were described by Pause (1877) and by Ernyei (1934)

Application of formaldehyde induced fluorescence technique (Eränkö 1952 1955 1967) to nervous tissues (Falck 1962) demonstrated the adrenergic innervation of the iris It has also been possible to locate the specific cholinesterase in the iris (Koelle et al 1952) Numerous light and electron microscopical studies on the autonomic innervation of the iris have been published recently For this reason the autonomic innervation of the pig iris (Werner 1962 Lukás 1964 Niemi & Tarkkanen 1964 Lukas & Čech 1965 1966) will not be dealt with in this study

Myelinated and non myelinated nerves could not be definitely distinguished from each other with the silver impregnation and methylene blue techniques earlier used. With silver impregnation myelin sheaths are more difficult to stain in peripheral nerves than in the central nervous system on account of the affinity of their connective tissue for the silver (Carleton & Drury 1957)

Methylene blue stains the total number of axons in the iris (Ehinger & Gustafsson–Sporrong 1966 Ehinger & Falck 1966) The information available on the sensory innervation of the iris is therefore partly outdated The myelinated nerves of the iris have not been extensively investigated electron microscopically

OBJECT OF THE INVESTIGATION

The purpose of the present investigation was

1 To study the vasculature and myelinated nerves of the pig iris by adopting and further developing the flat mount technique for this purpose

2 To study the gross vascular supply of the pig eye with special reference to the iris vessels

3 To study the architecture organization and structure of the blood vessels of the pig iris with light and electron microscope

4 To study the myelinated nerves of the pig iris and their architectural relation to the iris vessels

MATERIAL AND METHODS

Material

Altogether 565 fresh eyes from Finnish cross bred pigs females and castrated males aged about 6 months and 60–70 kg of body weight from the Helsinki City Abattoir were used

Methods

MACROSCOPICAL EXAMINATION

Using a millimetre measure the distances were recorded along the surface of the sclera between the optic nerve and the point where the long posterior ciliary artery reached the ocular surface and between the limbus and the point at which the long posterior ciliary artery pierced the sclera Similarly the distances were measured from the point of emergence of the superior and inferior vortex veins to the limbus and to the long posterior ciliary artery respectively (III)

FLAT PREPARATION METHOD

The eye fixed in 10 % neutral formalin for a minimum of 24 hours was opened equatorially the vitreous and the lens were removed and the anterior uvea was freed in toto The residue of the vitreous the pigmentary layer of the iris and the ciliary processes were removed The preparation was washed overnight in distilled water It was kept in 0 25 % potassium permanganate solution at room temperature for 4 hours and washed in distilled water kept in 5 % oxalic acid solution for 6 min washed in water and stained with PAS-hematoxylin (I II IV V)

TRYPSIN DIGESTION AND BLEACHING

After formalin fixation the flat preparation was made as described above and washed overnight in distilled water The preparation was incubated at 37° C in a solution of 3 % trypsin (Difco 1 250) in 0 1 M tris buffer (pH 7 8) for one hour to 12 days when the method was being developed (II) and later for 13–20 hours (III IV V) The preparation was washed *in distilled water It was kept in 0 25 %* potassium permanganate solution for four hours and washed in distilled water kept in 5 % oxalic acid solution for six min and washed in distilled water and stained with PAS hematoxylin (II IV V) Alcian blue (ICI) (II IV) Alcian blue (ICI) – PAS-hematoxylin (III IV) Sudan black or osmic acid staining (IV) The PAS hematoxylin and Sudan black staining methods were compared for studying the staining quality of the myelinated nerves (IV) For control purposes the digested unbleached preparation was stained with PAS hematoxylin (II)

THINNED FLAT PREPARATION

The iris was digested for 3–5 hours in trypsin solution (II V) bleached with 0 25 % potassium permanganate and 5 % oxalic acid and floated on a slide The anterior (II V) or posterior (V) part of the iris stroma was removed with small scissors and the preparation was stained with PAS *hematoxylin (II V) or Alcian blue (ICI) – PAS hematoxylin (V)*

INJECTION–DIGEST–BLEACHING METHOD

Indian ink containing 10 % carbon black (particle size 200–500 A) 4 3 % fish glue and 0 9 % phenol in water (batch *C 11/1431* a Gunther Wagner Pelikan) 5 % aqueous solution of Soluble Berlin blue (III V) or Neoprene latex (572 coloured blue 572 coloured red Du Pont Co Ltd Elastomers Research Laboratory) (III IV V) was injected into the long posterior ciliary artery or vortex vein of fresh pig eye from a 2 cc plastic syringe attached to a 2R2 0 4–11 mm injection needle The eye was *fixed* in 10 % neutral formalin for a minimum of 24 hours the flat preparation was made digested for 20 hours in trypsin solution bleached as described earlier and stained with PAS-hematoxylin (III IV V) or examined without staining (V)

SERIAL SECTIONS

The serial frozen sections (V) were cut at 6 to 10 µm and stained with hematoxylin eosin PAS-hematoxylin and Weigert van Gieson

For paraffin sections the eyes were fixed in 10 % neutral formalin (III IV V) *or in Zenker s fluid (III V) and serial sections were cut at 5 to 8 µm* The paraffin sections were stained with hematoxylin-eosin PAS-hematoxylin Weigert van Gieson (III V) Nassar s silver stain (III IV V) myelin stain (III) Mallory s aniline blue Weigert s resorcin fuchsin elastic stain (V) Bodian s (1936) method for nerve fibres and nerve endings or with a combined staining for fibres and cells of the nervous system (Kluver & Barrera 1953) (IV)

ELECTRON MICROSCOPY

As soon as the pig had been killed the eye was enucleated the iris dissected free and cut into small pieces Fixation was carried out in 3 % glutaraldehyde (Sabatini et al 1963) and postfixation in 1 % osmium tetroxide Dehydration with ethyl alcohol was followed by embedding in Epon 812 (Luft 1961) (IV VI) or Araldite (VI) Sections were cut with a Porter–Blum MT 1 ultramicrotome Thin sections for electron microscopy were stained with lead citrate (Reynolds 1963) or double stained with uranyl acetate (Watson 1958) and lead citrate Electron micrographs were taken with a UEMB 100 B (IV VI) or Siemens Elmiskop I (VI) electron microscope at original magnifications of 2000 to 90 000 (IV) and of 1000 to 19 000 (VI)

RESULTS AND COMMENTS

Flat mount technique for studying blood vessels and myelinated nerves of the pig iris

After potassium permanganate and oxalic acid bleaching the major arterial circle and the radial iris vessels (I) and their vascular wall structure (V) were brought out with PAS-hematoxylin staining The myelinated nerves *stained dark purple with PAS-hematoxylin*

Trypsin digestion brought out neither blood vessels nor nerves in unbleached PAS-hematoxylin stained flat preparations of the pig iris (II) After 20-hour digestion and bleaching the major arterial circle the radial vessels and myelinated nerves of the iris were visualised with PAS hematoxylin (II IV V) The background stained evenly and thinly and the myelinated nerves were visualised from an individual myelinated nerve fibre in the sphincteric region to the long posterior ciliary nerve

Blood vessels were demonstrable up to the capillary net with PAS-hematoxylin or Alcian blue (ICI)-PAS-hematoxylin in flat preparations thinned after 3–5 hour trypsin digestion and bleaching The structure of the vessel wall was visualised better than in an unthinned preparation digested for 20 hours bleached and PAS hematoxylin stained (II) The endothelial cells and circular smooth muscle cells were discerned in the arterioles Endothelial cells and pericytes were seen in the capillaries and venules (V)

The injection digest bleaching method revealed the vasculature of the iris up to the capillary net PAS-hematoxylin stained the myelinated nerves as a separate plexus in addition to the iris vessels (III) Without PAS hematoxylin staining the gross configuration of the iris vessels and their interconnections were brought out undisturbed by staining of other parts of the stroma (V)

Comments

The nonvascular components of the retina were digested well by trypsin (Kuwabara & Cogan 1960) The pig iris contains abundant trypsin resistant tissue such as chromatophores collagen fibres and sphincter muscle Thus it is impossible to separate the pure vascular net of the iris by digesting the nonvascular components with trypsin By combining digestion and bleaching the blood vessels and myelinated nerves were brought out (II)

Kuwabara and Cogan (1963) using trypsin digestion of the retina observed mural cells in the capillaries but did not see them in the capillaries of connective tissue conjunctiva or choroid Using digested flat preparations Ring and Fujino (1967) found only endothelial cells and no mural cells in the choroidal capillaries Ashton and Oliveira (1966) confirmed that the mural cells of the retina are intramural pericytes They found vascular pericytes in flat preparations of conjunctiva and of dermal and peritoneal connective tissue The present study was the first to show in digested flat preparations pericytes in the iris capillaries and venules and circular smooth muscle cells in the iris arterioles

Histological serial sections reveal only short distances along the individual vessels and give little impression of the whole vascular tree of the iris Flat preparations (I V) and flat preparations thinned after 3–5 hour digestion and bleaching (II V) revealed histologically three dimensionally the microvascular bed of the iris in its continuity and also some structural details of the vessel wall in each topographical portion

With injection digest bleaching preparations (III V) the architecture of the iris vessels was ascertained It was seen also stereoscopically When different contrast media were injected into the arteries and veins respectively the arterial and venous vascular trees were separated PAS-hematoxylin stained the myelinated nerves as a separate plexus apart from the blood vessels

GROSS VASCULATURE SUPPLYING THE PIG IRIS (III V)

The long posterior ciliary artery reaches the pig eye 5–13 (mean 10) mm nasally and 1–3 (mean 2) mm temporally to the optic nerve It runs along the external surface of the sclera nasally in the horizontal meridian and temporally slightly lower piercing the sclera 10–15 (mean 11) mm nasally and 6–10 (mean 8) mm temporally to the limbus (III) It divides into two branches which form the majo arterial circle in the ciliary part of the iris

The veins in the pig eye run radially from the iris to the ciliary body and become narrower in the iris root (V) They join the vessels passing to the vortex veins In the anterior choroid there is a profuse network of anastomoses between the branches of the adjacent vortex veins (III) The pig has four vortex veins one in each quadrant of the eye The superior vortex veins are situated on an average 13 mm and the inferior on an average 10–11 mm behind the limbus

Comments

Barth (1927) regarded as principal veins (venae vorticosae) the pig eye vessels running nasally in horizontal meridian and temporally slightly lower down This study (III) showed that these vessels are the long posterior ciliary arteries They run along the external surface of the sclera to the anterior part of the eye where they pierce the sclera (III) Similar results were reached in eyes of the albino rabbit (Scullica 1962) and cat (Wong & Macri 1964) Kiss (1943) considered that the radial iris veins after having reached the ciliary body branch out to form a new capillary net as in the portal circulation This study (V) showed that the venous trunk narrows as it enters the ciliary body but does not form a second capillary network conforming to the portal circulation It was found (III) that there is a profuse network of anastomoses between the branches of the adjacent vortex veins The results were similar in the albino rabbit eye (Scullica 1962) The present results (III) showed that the superior vortex veins leave the pig eye 13 mm and the inferior vortex veins 10–11 mm away from the limbus This is in good agreement with the observations made in cat

(Wong & Macri 1964) and rabbit (Leber 1903) eyes From the human eye however the superior vortex veins emerge 7–8 mm and the inferior vortex veins 5 5–6 mm behind the equator (Leber 1903 Duke–Elder & Wybar 1961)

MINUTE VASCULATURE OF THE PIG IRIS (V)

Vascular architecture of the pig iris

The major arterial circle of the iris branches partly into 2–3 circular arteries The main branches of the major arterial circle coming from the nasal and temporal sides of the iris do not fuse in the upper and lower part of the iris The recurrent choroidal arteries anastomose with the short posterior ciliary arteries

The radial iris arteries run zigzag or corkscrew wise and already branch in the ciliary part of the iris They show both sidearm and dichotomous branches

The precapillary arteriole is a smaller sidearm branch or a direct smaller arteriolar continuation of the radial iris artery The precapillary arterioles often have a straighter course than the curved radial iris arteries Sometimes a precapillary arteriole runs direct into a postcapillary venule forming the arterio-venous bridge No minor arterial circle was seen in the pig iris

The ciliary part of the pig iris has a relatively rich capillary vasculature The superficial capillary network continues in the pupillary part where it also follows the course of the connective tissue fibres The sphincter muscle is surrounded by a rich capillary network There are often almost knot like curves in the capillaries of the pupillary part

The capillaries in the pupillary part fuse and widen forming postcapillary venules which show bends and run towards the ciliary part In the ciliary part of the iris there are also postcapillary venules which may join the radial venous trunks or run without joining them into the ciliary body

The venous trunk shows bending in the pupillary part but in the ciliary part it runs fairly straight radially Two or three venous trunks may unite in the ciliary part Very rarely is a circular section of venous trunk seen The venous trunks run posteriorly to the major arterial circle into the ciliary body

Structure of pig iris blood vessels

The lumen is lined with endothelial cells whose elongated nuclei are arranged longitudinally along the vessel. The major arterial circle showed 1-2 layers, the radial iris arteries one layer, and the precapillary arterioles an incomplete layer of circular smooth muscle cells. Endothelial cells and pericytes were noted in the capillaries and postcapillary venules and in the radial iris veins.

In the major arterial circle the adventitia and connective tissue fibre sheath together form a thick layer. In smaller vessels there is a thick adventitia and around it a stromal sheath of connective tissue fibres. With hematoxylin-eosin and PAS-hematoxylin the adventitia stained almost hyaline-like. Weigert-van Gieson staining revealed profuse collagen fibres in the adventitia and connective tissue fibre sheath. Argyrophilic fibres were visualised with Nakar's silver stain in the adventitia. In the connective tissue fibre sheath some fibres had the appearance of black streaks when stained with Weigert's resorcin fuchsin elastic stain. Mallory's aniline blue staining revealed a partial circular tissue space between the adventitia and connective tissue fibre sheath and showed that the collagen fibres of the connective tissue fibre sheath extended to the iris stroma.

Comments

The present results agree with the observations of H. Rohen (1951) who noticed the superficial capillary network in the pig iris and the major arterial circle in its ciliary part. This study lends support to the observation of H. Rohen that the iris vessels are arranged according to the course of the connective tissue fibres. This prevents rupture of the vessels and blockage of the vessel lumen during pupillary movements.

François et al. (1955) claimed that there are no anastomoses between the major arterial circle of the iris and the choroidal arterial meshwork and no arterioles in the pars plana. The present findings support the observations of Wybar (1954) and Ring and Fujino (1967) who stated that the short posterior ciliary arteries and the recurrent choroidal arteries anastomose. This makes the collateral circulation to the iris and ciliary body possible.

The present observations agree with those of Eisler (1930) and Purtscher (1963) who described a complete media in the greater arteries of the iris and scattered circular smooth muscle cells in the smaller arterioles but not

with Ikui et al (1960) who denied the presence of smooth muscle cells in the iris arterioles The observations here made on the structure of the iris capillaries and postcapillary venules agree with those of Purtscher (1963) Castenholz (1971a) used the silver nitrate injection technique and reached similar results in the albino rat iris

ULTRASTRUCTURE OF THE MICROCIRCULATORY BED OF THE PIG IRIS (VI)

The major arterial circle 50–100 µm in diameter consists of a single layer of endothelial cells bulging into the lumen a partial elastica interna and usually two layers of smooth muscle cells The radial iris arteries are terminal arterioles measuring 15–50 µm in diameter with only one layer of smooth muscle cells and lacking an elastica interna The precapillary arterioles have a diameter of 7–15 µm and their media is incomplete The iris capillaries are muscle capillaries less than 8 µm in lumen diameter They contain non fenestrated endothelial cells a basement membrane and occasional pericytes The postcapillary venules are 8–30 µm and the radial venous trunks 30–90 µm in diameter They consist of endothelial cells basement membrane and pericytes (Table 1)

Comments

The microcirculatory bed of the pig iris was divided into different parts according to the terminology of Zweifach (1961) and Rhodin (1967 1968)

Previous authors found no muscle cells in the iris vessels (Tousimis & Fine 1959 Ikui et al 1960 Tomita 1960 Cunha–Vaz et al 1966 Purtscher 1966 Shively & Epling 1969) or were unable to demonstrate definite muscle cells in their electron micrographs (Lai 1967 Vegge & Ringvold 1969) Hogan et al (1971) described longitudinal muscle cells in the arterioles of the human iris It was possible in the present study to confirm electron microscopically the presence of circular smooth muscle cells in the arterioles of the pig iris the ultrastructure of these cells was consistent with earlier descriptions of vascular smooth muscle cells (Rhodin 1962 1967)

Pericytes have been found in the iris blood vessels besides endothelial cells and the basement membrane (Ikui et al 1960 Tomita 1960 Purtscher 1966 Cunha–Vaz et al 1966 Lai 1967) The essential morphological

identity of the pericytes of the iris vessels with the vascular pericytes of the conjunctiva retina and brain was pointed out by Ashton and Oliveira (1966) when describing the nomenclature of the pericytes Hogan et al (1971) however found no pericytes they reported only endothelial cells in the iris capillaries and venules and scattered muscle cells in the veins In this study endothelial cells basement membrane and pericytes were demonstrated in the capillaries and venules These results agree with the observations on mammalian capillaries and postcapillary venules (Rhodin 1968 Hammersen 1971)

Non fenestrated endothelial cells arranged in a layer have been observed earlier in the blood vessels of the human iris (Ikui et al 1960 Lai 1967 Vegge & Ringvold 1969) and in the capillaries of the rat iris (Cunha–Vaz et al 1966) A conflicting observation was made by Castenholz (1971 a b) who studied also the rat eye and reported fenestrations in the endothelial cells of the iris capillaries and venules The present study revealed only non fenestrated *endothelial cells in the whole microcirculatory* bed of the iris

Vegge and Ringvold (1969) observed zonula occludens between adjacent endothelial cells in all types of iris vessels In the present study (VI) the contiguous endothelial cells had a tight junction (Fawcett 1966) in the major arterial circle The intercellular junctions of the endothelial cells became gradually weaker towards the capillaries and postcapillary venules These capillaries and venules were seen to contain intercellular spaces of variable *width between contiguous endothelial cells* as observed earlier in the iris capillaries (Cunha–Vaz et al 1966 Lai 1967) and they also contained macula occludens formations which corresponded with the endothelial cell junctions in the capillaries of cardiac and skeletal muscle (Karnovsky 1967)

Table 1 Fine structure of the microcirculatory bed of the pig iris

		Major arterial circle	Radial iris artery	Precapillary arteriole	Capillary	Postcapillary venule	Radial iris vein
Diameter		100–50 μm	50 15 μm	15–7 μm	< 8 μm	8–30 μm	*30–90 μm*
Endothelial cells	(1)	non fenestrated bulge into the lumen	non fenestrated bulge into the lumen	non fenestrated bulge *into the lumen*	non fenestrated flattened	non fenestrated flat	non fenestrated flat
Endothelial cell junctions	(2)	tight junctional	tight junctional	part of tight junctional type	relatively wide intercellular space macula occludens	intercellular space *100–200 Å macula* occludens	wider tight junctional contact
Basement membrane	(3)	+	+	+	+	+	+
Elastica interna	(4)	+		–	–	–	–
Smooth muscle cells	(5)	two layers	one layer	incomplete layer	–	–	–
Pericytes	(6)	–		–	+	+	+
Adventitia	(7)	+	+	+	+	+	+
Stromal sheath *of connective* tissue fibres	(8)	strongly developed	+	+	+	+	+

Staining of myelinated nerves in flat preparations

After potassium permanganate and oxalic acid bleaching (I) the myelinated nerves were visualised with PAS hematoxylin staining After trypsin digestion and potassium permanganate bleaching the myelinated nerves stained purple with PAS hematoxylin blue with Alcian blue (ICI) (II) black with Sudan black staining and dark with osmic acid staining (IV) In a digested and bleached *flat preparation of the pig iris* the course of the myelinated nerves was brought out with PAS hematoxylin in the same way as in the same preparation after a second potassium permanganate bleaching and Sudan black staining

The course of myelinated nerves in pig iris

The long posterior ciliary nerve enters the iris with the long posterior ciliary artery It sends a rich plexus of myelinated nerves into the ciliary part of the iris The circular nerve bundles of the ciliary part send gently curving or radial corkscrew shaped branches towards the pupillary part There are also single myelinated nerve fibres in the ciliary part of the pig iris In the pupillary part the myelinated nerves on division and intersection form rhomb shaped configurations at first with a large mesh but closer to *the pupillary margin with a small mesh*

The myelinated nerves do not follow the course of the blood vessels in the pig iris They are arranged in conformity with the system of connective tissue fibres

Structure and ultrastructure of the myelinated nerves of the pig iris

Myelinated nerve bundles contain several myelinated nerve fibres which in the digested and bleached flat preparations were of two thicknesses The thinner ones occurred all over the iris the thicker mainly in the nasal and temporal parts of the iris

The myelinated nerves did not manifest themselves well in ordinary formalin fixed paraffin sections In the glutaraldehyde and osmium fixed

sections stained with toluidin blue there were myelinated nerve bundles in the ciliary part of the pig iris An electron micrograph of a thin section from the same area of specimen revealed myelinated nerves The nerve bundle was surrounded by a perineural sheath

The Schwann cell carried only one myelinated axon connected by the outer mesaxon to the Schwann cell surface The axon was surrounded by the myelin sheath which was fragmented and the node of Ranvier was seen between fragments The axoplasm contained mitochondria axofilaments axoplasmic vesicles and neurotubules and was surrounded by axolemma connected by the inner mesaxon to the myelin sheath

A concentric lamellar periodic structure was seen in the myelin sheath In the region of compact myelin the thickness of each layer consisting of a major dense line and a less dense band was on the average 124 Å

Comments

Intracellular lipid is not fixed in formaldehyde While such lipid is stained with appropriate lipid stains it will be dissolved by high-grade alcohol and xylene (Carleton & Drury 1957) So the myelinated nerves did not manifest themselves well in the ordinary formalin fixed paraffin sections (IV) because the myelin sheaths were dissolved during dehydration and clearing In the glutaraldehyde and osmium fixed thick section they were brought out Electron micrographs of an adjacent thin section revealed a typical ultrastructure of the myelinated nerves (IV) which is consistent with the description given by Babel et al (1970) Thus there is no doubt that the nerves revealed by flat preparations in this study were myelinated (Cogan 1971)

GENERAL DISCUSSION

Functional significance of the iris vascular patterns

The vasculature of the iris is part of the ciliary circulation (Duke-Elder & Wybar 1961) The arterial blood reaches the pig iris mainly along the long posterior ciliary arteries They have a thick media (III) The contraction of its circular smooth muscle cells controls the luminal size and the blood volume flowing to the anterior part of the eye

Non myelinated nerves were seen in the adventitia of the major arterial circle (VI) It has been shown that the iris vessels are purely sympathetically innervated (Ehinger & Falck 1966 Takkunen 1971)

This study (V VI) revealed circular smooth muscle cells in iris arterioles By vital microscopy Castenholz (1971a) showed constriction after noradrenaline infusion in arterioles of the albino rat iris while there was no change in the diameter of the iris capillaries and venules

At the points where the radial iris and ciliary body arteries branch off from the major arterial circle and the precapillary arterioles from the radial iris arteries the circular smooth muscle layer is often thicker and functions in the manner of a sphincter which appears in this region as a narrowing of the lumen Noradrenaline had a constricting effect on these arteriolar and precapillary sphincters (Castenholz 1971a) Constriction of the smooth muscle cells including the functional sphincters of the iris arterioles guides the blood flow to the different vascular branches regulates peripheral resistance reduces the arteriolar pressure functions as a protection for the capillary network and may completely close the vessel if necessary It also contributes to explain why the iris usually does not bleed during operation

Henkind (1965) suggested a possible reciprocal relationship between the arterial blood flow to the ciliary processes and the iris He pointed out that in mydriasis the iris vessels kinked and the arterial flow to the iris may be hindered by increased resistance Castenholz (1966) showed

however that the blood flow in the albino rat iris was just as fast in mydriasis as in miosis It seems evident that the volume of the blood entering the iris is regulated not only by arterial pressure changes but also by the neurohumorally controlled tone of the vascular smooth muscle cells especially of the arteriolar sphincters

Gregersen (1961) came to the conclusion that the aqueous humour can pass freely in and out of the tissue spaces in the interior of the iris stroma In this study (VI) non fenestrated endothelium was seen in the whole area of the microcirculatory bed of the pig iris This observation does not support the opinion of Castenholz (1971b) that endothelial cell fenestrations in iris capillaries and venules in normal eyes may occount for the involvement of the iris vessels in the circulation of the aqueous humour However fenestrated endothelium was seen in some iris capillaries of patients with pseudoexfoliation and capsular glaucoma (A Vannas 1972)

A relatively wide intercellular space was noted at the intercellular junctions of the thin endothelial cells in postcapillary venules and capillaries (VI) This space gradually narrowed on approaching the arterioles and radial iris veins This may be the morphological basis of the vascular permeability gradient which has been reported on earlier (Rous et al 1930) The intercellular spaces of variable width in capillaries and postcapillary venules (VI) can explain the fact that small molecular substances pass from the vessel lumen into the aqueous humour and vice versa Thus the diffusion through the iris vessels in aqueous humour dynamics (Kinsey & Palm 1955) is made possible

The radial iris veins were found to be wide in this study (V) They can therefore also function as blood stores and partly regulate the venous return It was noted (V) that radial iris veins were narrowed before entering the ciliary body This may be assumed to emphasize the functionally important position of the microcirculatory bed of the iris The narrowing parts of the radial iris veins would function as outlet tubes from this highly specialized system

The myelinated nerves enter the pig *iris* along the long posterior ciliary nerve (III IV) It comprises sensory fibres derived from the ophthalmic division of the trigeminal nerve and postganglionic sympathetic fibres which are non medullated (Duke-Elder & Wybar 1961) The present observation *is corroborated by the fact that when the ophthalmic division of the* trigeminal nerve was severed intracranially some of the nerve fibres entering the iris showed degeneration (Schimert 1936) The myelinated nerves of the iris are in fact sensory branches of the trigeminal nerve (Krapp 1962)

The myelinated nerves were not found in this study (IV) to follow the course of the blood vessels Electron microscopic examination (VI) revealed only non myelinated nerves in the vascular adventitia Thus the *iris vessels are not accompanied by myelinated autonomic afferent fibres* that might act as the afferent limbs of vasomotor reflexes

Ganglion cells were not observed in the iris (Pause 1877 Ernyei 1934 Schimert 1936 Beatie & Stilwell 1961 Werner 1962 Lassmann 1964) nor were they found in the present study Thus it cannot be assumed that the oculomotor nerve sends preganglionic myelinated fibres to the iris In a careful neurophysiological and neuropharmacological study Schaeppi *(1966) found that the parasympathetic nerve supply in the pig iris was* entirely postganglionic The autonomic ground plexus of the iris is in fact a network of Schwann cells supporting bundles of non myelinated axons (Richardson 1964)

It was found (IV) that the myelinated nerves in the pig iris were arranged in accordance with the course of the connective tissue fibres This prevents the myelinated nerves from being broken during pupillary *movements*

CONCLUDING REMARKS

1 In flat preparations after potassium permanganate and oxalic acid bleaching the major arterial circle the radial iris vessels and the myelinated nerves were visualised in the pig iris by PAS-hematoxylin staining The blood vessels up to the capillary network could be seen in a thinned flat preparation of the pig iris after 3–5 hours of trypsin digestion and bleaching The myelinated nerves were clearly visible by PAS hematoxylin and Sudan black staining after 20 hours of trypsin digestion and bleaching The course of the vessels in the pig iris was confirmed by the injection digest bleaching method using Neoprene latex 5 % aqueous solution of Soluble Berlin blue and Indian ink as contrast media

2 The long posterior ciliary artery passed along the external surface of the sclera to the anterior part of the pig eye where it pierced the sclera The radial iris veins became narrower in the iris root but did not branch out into a new capillary net as they entered the ciliary body

3 The major arterial circle of the pig iris branched partly into 2–3 circular arterioles passing around the ciliary part of the iris The main branches of the major arterial circle coming from opposite sides did not fuse in the lower and upper part of the iris The recurrent choroidal arteries anastomosed with the short posterior ciliary arteries No uniform minor arterial circle of the iris was seen The ciliary part of the iris also showed a relatively rich capillary network

4 The ultrastructure of the blood vessels of the pig iris is here described for the first time The major arterial circle an arteriole 50–100 µm in diameter was found to consist of endothelial cells a partial elastica interna and usually two layers of circular smooth muscle cells The radial iris arteries terminal arterioles 15–50 µm in diameter consisted of endothelial cells basement membrane and one layer of circular smooth muscle cells The precapillary arterioles had a diameter of 7–15 µm and

their media was incomplete The capillaries of the iris were "muscle capillaries less than 8 µm in diameter with endothelial cells basement membrane and pericytes The postcapillary venules were 8–30 µm and the radial iris veins 30–90 µm in diameter and consisted of endothelial cells basement membrane and pericytes The narrow and thick endothelial cells in the major arterial circle became wider and thinner along the course towards the capillaries In the arterioles the endothelial cells were tight junctionally joined to one another whereas in the capillaries and postcapillary venules there was a relatively wide intercellular space between adjacent endothelial cells

5 In addition to the myelinated nerve trunks the ciliary part of the pig iris also showed individual myelinated nerve fibres The myelinated nerves had a pattern conforming to the system of the connective tissue *fibres of the iris They did not follow the course of the blood vessels* in the pig iris The myelinated nerve fibres in digested and bleached flat preparations of pig iris were of two thicknesses The thicker ones occurred mainly in the nasal and temporal part of the iris whereas the thinner were seen throughout the area of the iris In addition to these new light microscopical observations the ultrastructure of the myelinated nerves in pig iris was described for the first time

The functional significance of the vasculature and myelinated nerves of the iris is discussed on the basis of the anatomical findings observed

REFERENCES

Arnold J (1863) Ueber die Nerven und das Epithelium der Iris *Virchows Arch. path Anat* 27 345–374

Ashton N (1949) Vascular changes in diabetes with particular reference to retinal vessels *Brit J Ophthal.* 33 407–420

Ashton N & Oliveira F (1966) Nomenclature of pericytes Intramural and extramural *Brit J Ophthal.* 50 119–123

Babel J Bischoff A & Spoendlin H (1970) *Ultrastructure of the peripheral nervous system and sense organs* Atlas of normal and pathologic anatomy Thieme Stuttgart

Barth K A (1927) Der Bau der Iris des Schweines unter spezieller Berucksichtigung des Muskelapparates und der Funktionszustande *Albrecht v Graefes Arch. Ophthal* 119 60–76

Beatie J C & Stilwell D L Jr (1961) Innervation of the eye *Anat Rec* 141 45–61

Bodian D (1936) A new method for staining nerve fibers and nerve endings in mounted paraffin sections *Anat Rec* 65 89–97

Carleton H M & Drury R A B (1957) *Histological technique for normal and pathological tissues and the identification of parasites.* 3rd ed Oxford University Press London

Castenholz A (1966) Morphologische und funktionelle Studien am Iriskreislauf der Ratte Vitalmikroskopische Beobachtungen *Albrecht v Graefes Arch. Ophthal.* 169 109–132

Castenholz A (1971a) *Untersuchungen zur funktionellen Morphologie der Endstrombahn.* Technik der vitalmikroskopischen Beobachtung und Ergebnisse experimenteller Studien am Iriskreislauf der Albinoratte Steiner Wiesbaden

Castenholz A (1971b) The vascular system of the albino rat iris and its suitability for vital microscopy and experimental studies on microcirculation *Ophthal. Res* 2 358–366

Cogan D G (1971) Personal communication

Cunha-Vaz J C Shakib M & Ashton N (1966) Studies on the permeability of the blood retinal barrier I On the existence development and site of a blood retinal barrier *Brit J Ophthal.* 50 441–453

Duke-Elder S & Wybar K C (1961) The anatomy of the visual system In Duke-Elder S ed *System of ophthalmology* Vol II Kimpton London

Ehinger B & Falck B (1966) Concomitant adrenergic and parasympathetic fibres in the rat iris *Acta physiol scand.* 67 201–207

Ehinger B & Gustafsson-Sporron, B (1966) Adrenergic and cholinergic axons in the mouse iris *Experientia 22* 218

Eisler P (1930) Die Anatomie des menschlichen Auges In F Slueck & A Bruckner ed *Kurzes Handbuch der Ophthalmologie* Vol 1 pp 97–98 Springer Berlin

Emyei I (1934) Ein Beitrag zur Kenntnis der Nerven der Augenhaute *Albrecht v Graefes Arch Ophthal 132* 140–154

Eranko O (1952) On the histochemistry of the adrenal medulla of the rat with special reference to acid phosphatase (M D Thesis Helsinki 1952) *Acta anat* (Basel) *16* Suppl *17*

Eranko O (1955) Distribution of fluorescing islets adrenaline and noradrenaline in the adrenal medulla of the hamster *Acta endocr* (Kbh) *18* 174–179

Eranko O (1967) The practical histochemical demonstration of catecholamines by formaldehyde induced fluorescence *J roy micr Soc 87* Pt II 259–276

Falck B (1962) Observation on the possibilities of the cellular localization of monoamines by a fluorescence method *Acta physiol scand 56* Suppl *197*

Fawcett D W (1966) *The cell its organelles and inclusions. An atlas of fine structure* Saunders Philadelphia

François J Neetens A & Collette J M (1955) Microangiographie oculaire *Ophthalmologica* (Basel) *129* 145–159

Friedenwald J.S (1949) A new approach to some problems of retinal vascular disease *Amer J Ophthal. 32* 487–498

Fuchs E. (1885) Zur Anatomie der Iris *Klin Mbl Augenheilk. 23* 467–478

Gregersen E. (1959) The tubular tissue spaces surrounding the endothelial channels of the human iridic vessels Histology and postfoetal development of the tissue spaces *Acta ophthal* (Kbh) *37* 199–208

Gregersen E (1961) On the imbibition of the human iris stroma with the aqueous humour *Acta ophthal* (Kbh) *39* 623–625

Gutmann A (1903) Ueber Kollagenes und protoplasmatisches Gewebe der menschlichen Iris *Z Augenheilk 10* 8–15

Hammersen F (1971) *Anatomie der terminalen Strombahn.* Muster Feinbau Funktion Urban & Schwarzenberg Munchen

Henkind P (1965) Circulation in the iris and ciliary processes Possible reciprocal relationship *Brit J Ophthal 49* 6–10

Hogan M J Alvarado J A & Weddell J E (1971) *Histology of the human eye* An atlas and textbook Saunders Philadelphia

Ikui H Mimatsu T Maeda J & Tomita I (1960) Fine structure of the blood vessels in the iris Light and electron microscopic studies (preliminary report) *Kyushu J med Sci 11* 113–124

Karjalainen K (1971) Occlusion of the central retinal artery and retinal branch arterioles (M D Thesis Helsinki 1971) *Acta ophthal* (Kbh) Suppl *109*

Karnovsky M J (1967) The ultrastructural basis of capillary permeability studied with peroxidase as a tracer *J Cell Biol 35* 213–236

Kinsey V E & Palm E (1955) Posterior and anterior chamber aqueous humor formation *Arch. Ophthal. 53* 330–344

Kiss F (1943) Der Blutkreislauf des Auges *Ophthalmologica* (Basel) *106* 225–250

Klüver H & Barrera E (1953) A method for the combined staining of cells and fibers in the nervous system *J Neuropath. exp Neurol 12* 400–403

Knight G E (1966) Injection-digest method for studying retinal vessels. *Brit J Ophthal. 50* 144–146

Koelle G B Wolfand L Friedenwald J.S & Allen R.A (1952) Localization of specific cholinesterase in ocular tissues of the cat *Amer J Ophthal. 35* 1580–1584

Krapp J (1962) Elektronenmikroskopische Untersuchungen über die Innervation von Iris und Corpus ciliare der Hauskatze unter besonderer Berucksichtigung der Muskulatur *Z.mikr -anat Forsch. 68* 418–447

Kuwabara T & Cogan D G (1960) Studies of retinal vascular patterns Part I Normal architecture *Arch. Ophthal 64* 904–911

Kuwabara T & Cogan D G (1963) Retinal vascular patterns VI Mural cells of the retinal capillaries *Arch. Ophthal. 69* 492–502

Lai Y L (1967) The electron microscopic studies on human iris vessels *Bull. Yamaguchi med. Sch. 14* 329–342

Lassmann G (1964) Zum Problem der Nerven und Gefassversorgung der Iris des Kaninchens *Ophthalmologica* (Basel) *147* 467–484

Leber T (1903) Die Circulations und Ernahrungsverhaltnisse des Auges In Graefe-Saemisch ed *Handbuch der gesamten Augenheilkunde* 2nd ed Vol 2 Pt 2 Engelmann Leipzig

Luft J H (1961) Improvements in epoxy resin embedding methods *J biophys. biochem. Cytol. 9* 409–414

Lukas Z (1964) Die Cholinesteraseaktivitat und Innervation der inneren Augenmuskeln. *Z. mikr -anat. Forsch. 71* 331–338

Lukas Z & Cech S (1965) Histochemical localization of monoamine oxidase in the anterior segment of the eye and the adrenergic innervation of its tissues *Acta histochem.* (Jena) *21* 154–164

Lukás Z & Čech S (1966) Adrenergic nerve fibres and their relation to monoamine oxidase distribution in ocular tissues *Acta histochem.* (Jena) *25* 133–140

Niemi M & Tarkkanen A (1964) Cholinesterases monoamine oxidase and phosphorylase in the iris muscles. *Arch. Ophthal. 72* 548–553

Pause C H (1877) Ueber die Nerven der Iris *Albrecht v Graefes Arch. Ophthal. 23* Pt III 1–23

Prince J H Diesem C D Eglitis I & Ruskell G L (1960) *Anatomy and histology of the eye and orbit in domestic animals.* Thomas Springfield Ill

Purtscher E (1963) Bemerkungen zum Bau der Gefasse und der Gefasscheiden in der Iris *Albrecht v Graefes Arch. Ophthal. 166* 295–311

Purtscher E (1966) Elektronenmikroskopische Untersuchungen zur Unterscheidung der Gefassadventitia von der Gefasscheide in der menschlichen Iris *Albrecht v Graefes Arch. klin exp Ophthal 170* 349–354

Raitta C & Vannas S (1969) Fluoresceinangiographie der Irisgefasse nach Zentralvenenverschluss *Albrecht v Graefes Arch. klin exp Ophthal. 177* 33–38

Reynolds E.S (1963) The use of lead citrate at high pH as an electron-opaque stain in electron microscopy *J Cell Biol 17* 208–212

Rhodin J A G (1962) Fine structure of vascular walls in mammals with special reference to smooth muscle component *Physiol. Rev 42* Suppl *5* 48–81

Rhodin J A G (1967) The ultrastructure of mammalian arterioles and precapillary sphincters *J Ultrastruct Res. 18* 181–223

Rhodin J A G (1968) Ultrastructure of mammalian venous capillaries venules and small collecting veins *J Ultrastruct Res 25* 452–500

Richardson K C (1964) The fine structure of the albino rabbit iris with special reference to the identification of adrenergic and cholinergic nerves and nerve endings in its intrinsic muscles *Amer J Anat 114* 173–205

Ring H G & Fujino T (1967) Observations on the anatomy and pathology of the choroidal vasculature *Arch. Ophthal. 78* 431–444

Rohen H (1951) Der Bau der Regenbogenhaut beim Menschen und einigen Saugern *Gegenbaurs morph Jb 91* 140–181

Rous P Gilding H P & Smith F (1930) The gradient of vascular permeability *J exp Med. 51* 807–830

Sabatini D D Bensch K & Barnett R.J (1963) Cytochemistry and electron microscopy The preservation of cellular ultrastructure and the enzymatic activity by aldehyde fixation *J Cell Biol. 17* 19–58

Schaeppi U (1966) Postganglionic nature of parasympathetic innervation of pig iris sphincter *Amer J Physiol. 210* 91–94

Schimert J (1936) Untersuchungen über den Ursprung und die Endausbreitung der Nerven der Iris *Z Zellforsch. 25* 247–258

Scullica L (1962) Observations of uveal blood flow pattern in excised arterially perfused rabbit eyes *Amer J Ophthal 54* 1057–1064

Shively J N & Epling G P (1969) Fine structure of the canine eye Iris *Amer J Vet Res. 30* 13–25

Takkunen E (1971) Vital staining of the rat iris with methylene blue *Acta anat* (Basel) *78* 18–24

Tomita I (1960) Electron microscopic studies on the fine structure of blood vessels in the human iris *Acta Soc ophthal Jap 64* 1447–1459

Tousimis A.J & Fine B S (1959) Ultrastructure of the iris An electron microscopic study *Amer J Ophthal. 48* Pt II 397–417

Vannas A (1969) Fluorescein angiography of the vessels of the iris in pseudoexfoliation of the lens capsule capsular glaucoma and some other forms of glaucoma (M D Thesis Helsinki 1969) *Acta ophthal.* (Kbh) Suppl *105*

Vannas A (1972) Vascular changes in pseudoexfoliation of the lens capsule and capsular glaucoma A fluorescein angiographic and electron microscopic study *Albrecht v Graefes Arch. klin exp Ophthal 184* 248–253

Vannas, S Raitta C & Vannas A (1969) Fluoreszeinangiographie bei Dystrophia retinae pigmentosa *Klin. Mbl. Augenheilk. 155* 673–680

Vegge T & Ringvold A (1969) Ultrastructure of the wall of human iris vessels *Z. Zellforsch. 94* 19–31

Watson M L. (1958) Staining of tissue sections for electron mi roscopy with heavy metals *J biophys. biochem. Cytol. 4* 475–478

Werner G (1962) Zur Innervation der Musculi sphincter und dilatator pupillae *Z. mikr anat Forsch. 68* 61–78

Wolff E (1948) *The anatomy of the eye and orbit* 3rd ed Lewis & Co London

Wong V G & Macri F.J (1964) Vasculature of the cat eye *Arch. Ophthal. 72* 351–358

Wybar K C (1954) A study of the choroidal circulation of the eye in man *J Anat* (Lond.) *88* 94–98

Zweifach B W (1961) The structural basis of the microcirculation In A.A Luisada ed *Development and structure of the cardiovascular system* pp 198–205 McGraw–Hill Book Co New York

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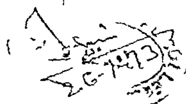
ACTA OPHTHALMOLOGICA
SUPPLEMENTUM 119

Epidemiologic Characteristics of Presumed Ocular Histoplasmosis

By

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CONTENTS

Preface 7

Abstract 8

Introduction

- Historical development 9
- Clinical features 11
- Therapy 12
- Experimental 13
- Epidemiology 14
- Need for further study 16

Material and Methods

- Background 19
- Selection of cases and controls 20
- Procedure 21
- Questionnaire 22
- Examination 23
- Expert's evaluation 30

Results 32

Discussion 50

Bibliography 57

PREFACE

The present study was carried out in the Department of Epidemiology Johns Hopkins University School of Hygiene and Public Health It formed part of a thesis submitted in conformity with the requirements for the degree of Doctor of Public Health

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A case control study of the association of *Histoplasma capsulatum* and disciform scars of presumed ocular histoplasmosis is described Cases were obtained from a group ophthalmic practice in Hagerstown Washington County Maryland Three groups of controls were used a group of individuals with fundus scars other than the cases a random sample of patients from the ophthalmic practice and a random sample from the 1963 Washington County census Cases and controls were selected from individuals aged 30–69 years and living in Washington County at the time of the examination Data were gathered from a self administered questionnaire a complete ocular examination serologic studies and delayed skin tests administered independently and read without knowledge of the individual s ocular status

Nineteen cases of disciform scars and 15 cases of peripheral scars of presumed ocular histoplasmosis were identified All disciform cases had a positive histoplasmin skin test (defined as 5 mm or more diameter of induration) compared with 60.0 % of those with peripheral scars and 60.7 % of controls On repeat histoplasmin skin test 93.3 % of individuals with peripheral scars were positive compared with 69.5 % of the controls People with disciform scars had larger mean induration size to histoplasmin greater frequency of positive reactions to the yeast complement fixing antibody test and greater likelihood of having calcification on pulmonary x ray attesting to the strong association in the past with *H capsulatum*

Disciform cases tended to live in wood frame houses to smoke cigarettes more heavily to have more frequent exposure to dust birds bats and guano to have a positive tuberculin skin test and to be lower on the socioeconomic scale These same risk factors for people with only peripheral scars were more similar in value to those of the controls

Peripheral lesions seem most likely to occur at the time of first exposure to and infection with *H capsulatum* whereas the disciform process probably occurs 10–30 years later

People who have disciform scars generally have a heightened cellular and serologic immune response to histoplasmin possibly resulting either from reexposure to the organism or from innate allergic hypersensitivity It is postulated that for the disciform process to occur there must be prior sensitization of the choroid by *H capsulatum* organisms the presence of an altered choroidal vascular permeability and a primed cellular immune system

Key words uveitis – choroiditis – histoplasmosis – epidemiology

Historical Development

Although histoplasmosis had been recognized as a systemic infection since 1906 when Darling(1) first described the entity the possibility of ocular involvement in this disease was not seriously considered until the last two decades It was only 10 years ago that a specific ophthalmic syndrome was proposed

In 1942 Reid(2) first described ocular abnormalities in this disease He found small white irregular areas surrounded by hemorrhages in both fundi of a patient dying of acute disseminated histoplasmosis These areas "were not unlike tubercles

Until 1945 histoplasmosis was considered a rare and uniformly fatal disease About this time Palmer(3) and Christie & Peterson(4) independently developed a histoplasmin antigen and showed that histoplasmosis was in fact a benign highly prevalent disease and a common cause of pulmonary calcification

This led Day(5) in 1949 to skin test the ward patients of the Wilmer Institute with histoplasmin He found that a statistically significant per cent of the uveitis cases were sensitive to the antigen when compared to other patients on the service Krause & Hopkins(6) in 1951 reported the flare up of a parafoveal atrophic scar coincident with a histoplasmin skin test In their case fresh hemorrhages occurred in the macular area causing marked reduction in visual acuity They suggested that benign histoplasmosis must be considered as another cause of granulomatous uveitis

Woods et al (7) in 1954 while analyzing a group of adult patients for toxoplasmic chorioretinitis found seven cases with posterior granulomatous uveitis who were anergic to tuberculin had pulmonary calcification and were strongly histoplasmin sensitive Woods also felt that histoplasmosis might cause uveitis but cautioned that until *Histoplasma capsulatum* organisms were isolated from a human eye Koch s postulates would not be fulfilled(8)

In 1958 Schlaegel(9) reported a second case of flare up of a chorioretinal scar following the histoplasmin skin test In a review of 100 patients from the uveitis clinic at Indiana University he pointed out that ocular disease associated with histoplasmosis would most likely involve the posterior portion of the eye as a localized chorioretinitis with little or no involvement of the anterior segment He also noted that this disease was found in older adults whereas chorioretinitis due to toxoplasmosis occurred more frequently in the under 40 age group

It remained for Woods & Wahlen in their classic papers of 1959(10) and 1960(11) to describe and define the picture of presumed ocular histoplasmosis They presented 19 patients who had both peripheral and central chorioretinal scars The peripheral lesions which could be located anywhere in the fundus but more usually away from the central area were described as discrete focal spots of atrophic chorioretinitis usually about one third disc diameter or less in size were often somewhat yellowish in color and were either depigmented or sparsely pigmented The central or disciform lesions were found "directly in the macula or closely contiguous to it" These disciform scars were so named because in the healed stage they had the appearance of either a "circular well outlined glial scar or an irregular mass of heaped up pigmented glial tissue beneath the retina

All nineteen patients in their series were reactive to histoplasmin antigen nine were also nonreactive to tuberculin and had pulmonary calcification on chest x ray Woods & Wahlen also reported the third flare up of an ocular scar coincident with a histoplasmin skin test These papers set the tone for most of the work done in the field of presumed ocular histoplasmosis during the suc ceeding ten years Again the need of fulfilling Koch s postulates was empha sized

Junius & Kuhnt(12) in 1926 presented a clinical entity characterized by hemorrhagic disciform detachment of the macula Two forms of this entity were subsequently distinguished a senile type(13) occurring in older indivi duals and presumably related to vascular degenerative disease and a second type occurring in younger adults(14 15) in which no underlying cause could be implicated In 1938 Verhoeff(16) in discussing the pathology of the juvenile type of Junius Kuhnt disease described a case in which a focus of lymphocytes was found contiguous to the macular hemorrhage Terry(17) one year later presented a similar case slides of which were reviewed by Verhoeff in this patient lymphocytic infiltration was found beneath the hemorrhage and at the disc margin

Salvin & Furcolow(18) described a patient in 1954 with acute retinitis in one eye and a possible cyst of the fellow retina This patient was otherwise asymptomatic but had a positive histoplasmin skin test and pulmonary apical fibrosis *H capsulatum* organisms were isolated from gastric aspirate in this patient

Maumenee in 1959(19) the same year as Woods classic paper noted that peripheral atrophic fundus scars were present in over 50 % of his patients with juvenile Junius Kuhnt disease

In several eyes small inflammatory foci of choroidal lymphocytes were found contiguous to the disciform lesion

The association of juvenile Junius Kuhnt detachment of the macula with benign systemic histoplasmosis was thus made by Woods in 1959(10) and was

further emphasized by Maumenee in 1965 (20 21) It should be pointed out that although not all cases of juvenile disciform disease are thought due to histoplasmosis a large proportion have been attributed to this disease

Clinical Features

Reports in the early 1960 s described small groups of patients with presumed ocular histoplasmosis(22–24) Later investigators added characteristics that further differentiated this entity from other types of granulomatous chorio retinitis Walma & Schlaegel(25) evaluated cases from their clinic and found that isolated disseminated scars rather than focal lesions were more likely to be present in the choroid of affected individuals Van Metre & Maumenee(26) in a review of their office records found a statistically significant association between a positive histoplasmin skin test and the specific ocular picture This was also found for histoplasmosis complement fixation tests and fibrocalcific changes on pulmonary x ray(27) They emphasized that vitreous or anterior segment inflammatory involvement was almost never present in this disease Schlaegel & Kenney(28) pointed out that peripapillary scarring could be found in 85 % of their patients with the disciform process They observed four distinct types of scars diffuse nodular hemorrhagic and mixed

Schlaegel et al (29) and Krill et al (30) have elaborated on the natural history of the peripheral scars These scars can be found in any area of the fundus but are more commonly found posterior to the equator The acute lesions have the appearance of soft yellow to orange nodular infiltrates in the inner layers of the choroid They may vary in size from small round barely visible dots to areas about the diameter of the optic disc The borders are usually slightly indistinct and there may be slight haze or ground glass appearance to the over lying retina

As these lesions resolve they leave atrophic and punched out appearing scars involving the inner layers of the choroid Often there is the suggestion of thin yellowish material in the base of these scars which obscures the under lying choroidal vessels Pigment clumps may be found within the scars or along their borders In an eye where old atrophic scars were already present Krill et al (30) documented by fluorescein angiography the development of a new peripheral *lesion in previously uninvolved choroid*

Numerous authors(10 22–30) have commented upon the clinical character istics and morphologic evolution of the macular and paramacular disciform lesions Gass(31) in 1967 summarized the current concepts relating to the pathogenesis of this entity The first change that can be seen clinically in the macular process is a focal yellowish white or grey circumscribed slightly elevated area of choroidal infiltrate similar to that seen elsewhere in the peripheral lesions The patient at this time usually notices impairment of vision and perceptual distortion of objects

As the macular disease progresses a focal disturbance of the overlying pigment epithelium develops causing these cells to proliferate This gives a dark green to black ring or doughnut shaped appearance to the choroidal lesion The presence of this pigmentary change usually heralds the onset of serous exudate either beneath the pigment epithelium or subretinally Hemorrhage will almost inevitably occur in the same areas

At this stage fluorescein angiography often demonstrates the presence of choroidal neovascularization beneath the proliferated pigment These vessels are felt to enter the disciform lesion from the choroid through breaks in Bruch s membrane It is possible that contracture of the scar tissue may subsequently rupture these vessels and induce new bleeding or when exacerbations occur these new vessels because their endothelial cells are not as competent may more readily allow serum and blood to leak through their walls The disciform process usually heals by forming a fibrovascular scar beneath the retina When this end stage is reached 86 % of the involved eyes have some permanent impairment of vision and 56 % are legally blind(29)

Hyvarinen Lerer & Knox(32) showed that in closely followed patients with presumed ocular histoplasmosis an active process can be seen developing immediately adjacent to or around an old peripheral scar This activity may be entirely asymptomatic and demonstrable only by fluorescein angiography They found that a number of these scars seen on angiograms could not be visualized with the ophthalmoscope Gass & Wilkinson(33) found that when the second macula becomes involved the new disciform process will frequently develop from or around an old peripheral atrophic scar This finding has also been confirmed by Schlaegel(34) who feels that the risk of getting the disciform disease is about tenfold if peripheral scars are present in the posterior pole

Therapy

Falls & Giles(35) in 1960 presented an initial enthusiastic study favouring the use of the antifungal drug amphotericin B in the treatment of the disciform lesion A second report by the same authors(36) was not as enthusiastic and a third report(37) five years later was quite discouraging Others(22-24 38 39) who have used the drug have found improvement in some patients but not in others Makley et al (40) in 1965 reviewed the previous literature and added additional cases of their own finding an overall 66 % therapeutic response reported However their personal experience with the drug was poor The full treatment with amphotericin B required at least a six week course of daily intravenous infusions given in a hospital Also the side effects of this drug frequently caused treatment to be stopped prior to completion

Other therapy has been proposed Histoplasmin desensitization was carried out in many patients on the premise that the disciform process might be the

result of hypersensitivity to the organism Woods(10 11) felt this might be the case because the central scar was found in eyes in which peripheral scars were quiescent and presumed to have occurred many years prior to the onset of the macular lesion This theory was also supported by the simultaneous occurrence of flare ups around old scars coincident with administration of histoplasmin skin tests(6 9 10) At present this form of therapy is only infrequently used because of its moderate benefit(40 41) and because excessive or too rapid a course of desensitization frequently excites hemorrhagic exacerbation of the disciform lesion(37)

Imuran (azathioprine) has been given in an attempt to reduce the immuno logic component to the disciform disease This drug was initially found to be effective but when therapy was discontinued the disciform lesion recurred and progressed through its natural course to the fibrotic state(42) The most recent approach to be advocated is photocoagulation of leaking choroidal blood vessels or tufts of choroidal neovascularization as demonstrated by fluorescein angiography(41 43–48) By this means further serous or hemorrhagic detach ment of the macula may possibly be prevented and eventual scar formation *minimized Although there has not been time for adequate evaluation of this* technique Watzke(49) who has conducted a small controlled therapeutic trial finds that after the treated patients have been followed for several years photo coagulation does not seem to offer any beneficial effect

Systemic glucocorticosteroids(41 50) in high dosage and for prolonged periods seem to be the main therapeutic regimen presently used by ophthalmo logists in attempts to dampen the inflammatory reaction. Again there have been no controlled trials showing this drug to be effective

Experimental

The earliest experimental work in ocular histoplasmosis was by Day(5) in 1949 When he injected viable *H capsulatum* cells either directly into the anterior chamber of rabbit eyes or intravenously a nodular granulomatous iritis was produced Spores injected into the vitreous caused localized abscesses

Smith(51) found that steroids or cold was necessary for growth of the or ganism in pigeon eyes This has not been confirmed by others(52 53) Oku daira & Schwarz(54) about the same time showed that in previously sensitized rats intraocular injection of either viable or heat killed spores could produce retinitis and choroiditis The inflammatory response to the injected organisms in the posterior part of the eye consisted of lymphocytic and histiocytic infil trates

Smith et al showed that intraocular injection of virulent yeast phase *H capsulatum* organisms could produce an anterior iritis in rabbits(55) and mon

keys(56) By intravitreal injection they produced a chorioretinitis of discrete yellowish nature(57 58) similar to that seen in peripheral lesions of humans

Schlaegel et al (59) in previously sensitized rabbits found yeast phase antigen to be a better stimulator of ocular reaction than mycelial phase antigen Sethi et al (60) showed amphotericin B effective in treating experimental anterior chamber histoplasmosis in rabbits Salfelder et al (61) by intraarterial injection of yeast cells in dogs were able to demonstrate involvement of most tissues of the eye a focal granulomatous lesion was produced in the choroid of several animals They found a strain difference in the ability of the *H capsulatum* organisms to infect the eye(61 62) In their study yeast cells could not be found two months after inoculation when looked for with special stains Campbell has also confirmed that some strains of *H capsulatum* are more virulent than others and have greater ability to disseminate to ocular tissue(63)

Wong & Green(64) have recently been able to produce peripheral ocular lesions in the choroid of rabbits following intravenous injection of *H capsulatum* spores These peripheral lesions were similar to those seen in the human disease However up to the present time no observer has been able to reproduce the macular disciform scar that is the hallmark of the human disease

Epidemiology

Almost all cases of presumed ocular histoplasmosis with disciform macular scarring have been found among the white race(29 34 40) Although the frequency of disciform macular involvement in the black race is rare the frequency of peripheral atrophic scars(65) and histoplasmin sensitivity(66) for blacks is equal to that of the whites This difference in frequency of peripheral and disciform lesions in the Negro is unexpected however it is not due to poorer medical surveillance because even in large clinic populations this disease is not found among indigent blacks(67)

The disciform disease is slightly more common among males than females (25 26 29 38) Asbury(65) found 1 8 % prevalence of peripheral scars among males and 1 2 % among females A similar sex prevalence (2 6 % and 2 4 % respectively) was found by Smith & Ganley in Walkersville Maryland(68) The male sex has greater sensitivity to histoplasmin(66 69 70) and a higher rate of acquisition of histoplasmin positivity than does the female sex(71)

The modal age of onset of first eye involvement with the disciform lesion is the fourth decade of life the disease most frequently occurs during the third to the sixth decades Although it has been found in children(72) the disease is rare before the age of 20 and it is also infrequent after the age of 59(25 26 28) In the Walkersville study where those aged 13 years and older were examined peripheral scars were found uniformly at all ages(68)

The third to sixth decade is the age in which the largest reactions to the

histoplasmin skin tests have been found(70) The Indiana University investigators have found that individuals who have the disciform lesions are more sensitive to delayed skin tests in general(73) and to the atypical mycobacteria in particular(74) They suggest that previous exposure to mycobacteria may provide a Freund s adjuvant effect on the subsequent development of the ocular lesion

Disciform scars tend to be bilateral in 24–33 % of cases seen in referral centers Schlaegel & Weber(75) find that the average interval between the first and second attack is 4 8 years Fifty two per cent of these patients also have bilateral peripheral atrophic scars This distribution of atrophic lesions is similar for those people with only peripheral scars in whom 54–60 % (65 70) *have involvement of both eyes Peripapillary scars are found in 85 % of pa*tients with disciform disease (28) and in only 4–28 % of people with peripheral scars(65 70)

From 93–100 % of patients described in the literature with the disciform process of presumed ocular histoplasmosis have positive histoplasmin skin tests (25–27 29 38 40 76) and 16–68 % of the cases have positive histoplasmin complement fixation tests(25–27 38 40 77) However skin testing may induce complement fixing antibodies(78) and in these studies blood was not necessarily drawn prior to injection of histoplasmin

From 50–81 % of patients with the disciform disease have pulmonary calcific nodules on x ray(25 38) and 85–90 % have fibrocalcific changes consistent with histoplasmosis(26 27) Presence of pulmonary calcification is considerably less in those patients with peripheral scars only (12 5 %) and not significantly different from the total population (15 4 %) Excellent reviews of the clinical and epidemiologic features of disciform lesions have been published by Schlaegel(79–81) and Leinfelder(82)

There have been two epidemiologic studies directed toward the problem of presumed ocular histoplasmosis The first by Asbury(65) in 1966 was a survey of a prison population in Ohio In this study he was not able to show an association of the eye lesion with a positive histoplasmin skin test but in those cases who were nonreactive all had calcified pulmonary nodules

The second study by Smith & Ganley(68 83 84) in 1970 was a community survey for fundus scars compatible with presumed ocular histoplasmosis They found a highly significant statistical association when the ophthalmologic *observations and the skin test readings were made independently between the* peripheral scars of presumed ocular histoplasmosis and a positive histoplasmin skin test One patient examined during this survey had macular disciform scarring From this one case a rough estimate of 0 1 % prevalence of this disease for the community was made The occurrence of peripheral scar cases was twenty six times more common (2 6 % prevalence) Asbury(59) found a prevalence of 1 6 % for people with inactive peripheral atrophic scars

By comparing data on peripheral scars with those characteristics described in the literature for people with disciform lesions a person at high risk of developing the disease might be hypothesized Caucasian male age 30 to 50 years having peripheral atrophic macular paramacular or peripapillary scars calcified pulmonary nodules positive histoplasmin skin test and living in an area endemic to *H capsulatum*

Need for Further Study

The normal course of successful investigation of the etiology of a disease usually proceeds as an orderly progression of events Beginning with the germ of an idea in an investigator s mind additional knowledge is added until proof of causality is demonstrated Either experimental models or finding the organism in pathologic specimens confirms the association

The early story of presumed ocular histoplasmosis followed a similar pattern It took about ten years from the time that it was first suggested that benign systemic histoplasmosis might cause ocular disease(5) until Woods & Wahlen (10) in 1959 described a distinct ocular picture The entity was further defined (19 28) the natural course of the disease clarified(29 30) and pathophysiologic mechanisms postulated(31)

At this point additional efforts to demonstrate a causal association of the ocular picture and benign systemic histoplasmosis were unsuccessful While intravenous injection of yeast cells in rabbits has produced peripheral choroidal lesions(64) the central disciform macular lesion has not been reproduced Also most experimental infections with *H capsulatum* caused inflammation of all areas of the animal eye iris choroid retina vitreous and extraocular muscles (51–61) This marked involvement has not been observed in the human disciform macular disease It was expected that the etiology would be confirmed by histological section of involved eyes but to date the only confirmed pathological specimen has been from a patient with purulent endophthalmitis much like that produced in experimental models(85)

Considerable circumstantial evidence has been marshalled to support the etiologic association of *H capsulatum* and the disciform lesion of presumed ocular histoplasmosis Numerous clinical reports have shown a high degree of association in patients having this syndrome with a positive histoplasmin skin test(10 22–29 41) Also most cases of presumed ocular histoplasmosis have come from areas where *H capsulatum* is endemic and histoplasmin sensitivity high particularly Ohio Indiana Illinois and Maryland Typical disciform scars have not been found to any extent in England where systemic histoplasmosis is rare(86 87) The 50 % prevalence of pulmonary calcification on chest x rays of patients with this ocular disease is also presumptive evidence

of an etiologic association since in an endemic area histoplasmosis is a more frequent cause of such calcification than tuberculosis(3 4 88)

The peripheral atrophic choroidal scars that are a component of the ocular syndrome have been reproduced in experimental animals(57 58 64) Smith & Ganley(68) have shown these same peripheral scars to be statistically associated with a positive histoplasmin skin test Asbury(65) however did not find this same association

The finding of granulomatous lymphocytic cellular infiltrates in disciform lesions submitted for pathologic examination(16 17 19 31) is consistent with host response to infection by *H capsulatum* Maumenee(76 89) recently presented a case in which yeast like cells were found in this inflammatory focus but it was not conclusively demonstrated that these cells were *H capsulatum*

With considerable evidence to the contrary the question of an etiologic association between infection with *H capsulatum* and the disciform macular disease of presumed ocular histoplasmosis is far from settled Early studies showing this association were not done blindly data were accumulated from office practices where the presence of a positive histoplasmin skin test was often a deciding factor in making the diagnosis Since most cases of this syndrome come from areas where positive histoplasmin skin tests may be found in 90 % of the general population(90) a high frequency of positive skin tests in the cases are to be expected

It can be postulated that some other factor having the same geographic distribution as *H capsulatum* might cause the ocular disease Such an entity could conceivably be *Blastomyces dermatitides* Its geographic distribution overlaps that of *H capsulatum*(91) infected individuals cross react with histoplasmin antigen(92) and one observer feels that *B dermatitides* may cause widespread unrecognized pulmonary disease similar to histoplasmosis(93)

Inability to reproduce the disciform disease in experimental animals has been used to discredit the role of *H capsulatum* in this syndrome however no one has attempted to duplicate the natural course of the disease in the animal model as it is presently understood in human cases Spaeth(94) in a chart review of culturally or histologically documented histoplasmosis cases from the files of Walter Reed Army Hospital and the National Institutes of Health could find no mention of the presence of disciform maculopathy in 134 cases reviewed Only one patient had what appeared to be peripheral atrophic scars These patients were not personally examined by the author nor by trained ophthalmologists

Another argument against the etiologic role of *H capsulatum* has been the lack of response of the ocular disease to specific anti fungal therapy However evaluation of therapeutic trials with amphotericin B has been confounded by the fact that several of these studies were conducted early in the evolution of the knowledge of the disciform disease and other entities such as toxoplasmic

chorioretinitis and choroidal melanomas were inadvertantly included among the cases Also the drug was used in some cases where the disciform process had reached the hemorrhagic state after which time irreversible fibrovascular scar formation usually occurred in these cases amphotericin B therapy could not be effective

The main reason for skepticism is that neither have Koch s postulates been fulfilled nor has the organism been unequivocably demonstrated in pathologic specimens from human disciform lesions Because the presence of the disciform scar alone is not sufficient reason for enucleating the eye because organisms cannot be found in the experimental peripheral lesion two months after in oculation and because the disease could have an allergic basis opportunity to test Koch s postulates may not be possible

There is a need then to re examine the etiologic association of *H capsula tum* and disciform macular scars of presumed ocular histoplasmosis The present study was designed to challenge this association by a double blind case control approach Several characteristics were evaluated (1) histoplasmin sensitivity (2) induration response to histoplasmin skin test (3) complement fixing antibodies (4) pulmonary calcification and (5) opportunity for exposure to the organism Several risk factors were also examined that had been sug gested might play a role in this disease allergic tendencies smoking history occupation and place of residence

MATERIAL AND METHODS

Background

Washington County Maryland was selected as the locale for this study for several reasons Cases of presumed ocular histoplasmosis were known to have occurred in that area since several patients with the fundus scars had been referred to the Wilmer eye department Comstock et al (95) had previously found 54 % histoplasmin sensitivity among the County high shool students a level of sensitivity acceptable for testing the hypothesis The County had a good mixture of urban suburban and rural inhabitants as well as a broad representation of social economic and educational levels

As a result of a private census conducted in 1963 certain demographic and social characteristics of most individuals within the County were on file at the Johns Hopkins Training Center for Public Health Research in Hagerstown These data were used in the present study to compare cases and controls The County has only a moderate inward and outward mobility so that 95 % of those selected for the study could be located in the census files

The Johns Hopkins Training Center facilities were utilized as a base of operations to select cases and controls to contact the study group and to con duct patient examinations The training center was also used for card coding keypunching and data analysis

The two hospitals of the county are located in Hagerstown the largest city and county seat and the focal area for specialized medical services among most county inhabitants This is especially true for ophthalmology as all ophthal mologists in the county have their offices in Hagerstown The nearest ophthal mic practice outside the county is located in Chambersburg Pa and this physician refers many of his problem cases to Hagerstown for evaluation There are six practicing ophthalmologists in Hagerstown The original intent was to use the records of all ophthalmologists to obtain an estimate of pre valence but two refused to open their files Neither of these physicians had large practices and one was semi retired The study was therefore limited to the group practice of Drs James Sachs William Beckner Robert Russell and Leslie Bard

Their office records consisted of 5 × 8 index cards sometimes several stapled together stored alphabetically in 96 file drawers These files had recently been updated to exclude any patient who had not been seen in the office within the past fifteen years It was roughly estimated that there were

approximately 48 000 patients records on file A sample of these records indicated that about 66 % of their patients lived within Washington County (32 000 patients) this represented one third of the total population of the county The remainder of their patients came from West Virginia Pennsylvania and Frederick County Md

Selection of Cases and Controls

Each record was examined for mention of peripapillary scarring macular edema (central serous retinopathy) macular scarring that appeared to be elevated and cystic hemorrhagic lesions of the macula People who had mention of any of these abnormalities on their case records were identified as potential cases Individuals were excluded from the study if the clinical record noted the presence of diabetes mellitus hypertension ocular trauma or aqueous and vitreous inflammatory cells Additional potential cases were added currently as they appeared in the ophthalmologists office and had lesions felt to be consistent with the disease

When review of the office files showed potential cases under the age of 30 to be rare it was decided to limit the study to individuals 30 years of age or older on January 1 1970 There were 210 people identified as potential cases It was also required that cases and controls live in Washington County at the time of the examination Residency requirements were determined by consulting the telephone book city directory or 1963 census Of 210 individuals identified as potential cases only 177 met the final requirements of the study and were therefore considered as eligibles By means of ophthalmic examination members of this group would subsequently be subdivided into either true cases or a control group composed of fundus scars other than those deemed compatible with presumed ocular histoplasmosis

Two additional control groups were also selected one group was drawn from the office records of all patients who had been examined by the four ophthalmologists within the past 15 years the second was a population control group drawn from the 1963 Washington County census listing To obtain the office controls the following two step sampling procedure was carried out Beginning with the tenth patient record of the first file box the name address age and phone number was recorded on every twentieth patient No distinction was made as to the type of problem that brought the person to the ophthalmologist Each patient card was coded numerically beginning with the number 001 By use of a table of random numbers a subset of 100 controls was selected who were 30 years of age or older and were living in the county at the time of examination Ten of the selected individuals at the time of the study had died moved or were otherwise unable to be located an additional ten names were randomly drawn from the files to form a group of 100 individuals Thus a total

of 110 office controls were drawn of whom 100 were found eligible for participation in the study

Population controls were selected from the 1963 census tables by a systematic sample drawn from an alphabetical listing of people who lived in Washington County July 15 1963 After a random start every two hundredth name was selected or the nearest following name of an individual who would be 30 years or older by January 1 1970 This group of approximately 460 names was numbered consecutively and from this a subgroup of 100 individuals currently living in Washington County was picked by use of a book of random numbers Four individuals selected could not be located through the post office or telephone information system and six had moved out of the county These ten people were excluded from the study and additional people were randomly selected to obtain a final census control group of 100 individuals

Procedure

To prevent bias in either the order of bringing people in to be examined or in the actual examination of the individual letters from a master list were sent out alphabetically to all potential cases and controls describing the study No note was made as to which study group the individual belonged Each person on the master list was called by the secretary at the Training Center or by a research assistant and an appointment was scheduled for the time and place of examination Examinations were held four days a week evenings included and on selected weekends so that convenient times would be available to everyone Transportation was provided for those needing it for those not desiring or able to come to the training center home visits were made

Table 1
Rates of participation by the three study groups

	Number eligible	Number participating	Per cent participating
Potential cases	177	138	78 0
Office controls	100	84	84 0
Census controls	100	65	65 0
Total	377	287	76 1

χ (2 df) = 10 49 01 > p > 001

Table 2

Comparison of participants and refusals among census controls as previously examined by group practice of ophthalmologists

Status in present study	Previously examined by ophthalmic group					
	Examined		Not examined		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
Participants	27	41 5	38	59 6	65	65 0
Non participants	6	17 1	29	82 9	35	35 0
Total	33	33 0	67	67 0	100	100 0

χ (1 df) = 6 2? 02 > p > 01

If the person did not have a telephone but was verified by the post office as still living within the county a series of registered letters was sent out asking the individual to contact the Training Center for an appointment If they did not contact us they were kept in the study but counted as a refusal

Of 377 selected 287 (76 1 %) participated in the study The office controls had the best participation (84 %) as compared to the census controls (65 %) The potential cases were intermediate with 78 % participation These differences in rates of participation by the three study groups were significant at the 01 level (Table 1)

An important reason for non participation by the census controls might be the fact that 67 % of this group had not been seen by the ophthalmologists as patients in their office Of the 65 who did participate 27 (41 5 %) had been previously examined by the ophthalmologists whereas of the 35 non participants only 6 (17 1 %) had been seen previously (Table 2) The 33 % population sample seen by the ophthalmology group is quite similar to the 32 % of the total Washington County population estimated to have been examined by these ophthalmologists after review of their office files

Questionnaire

A self administered questionnaire was mailed to all who participated in the study This questionnaire was not pre tested it was partly pre coded and partly open ended The questionnaire was reviewed at the time of examination to insure completeness of answers by any of four individuals who assisted with

the technical portion of the study a dental student on a summer epidemiologic training fellowship a nurse who also administered and read the skin tests a research assistant at the training center or the author on rare occasions

Examination

The examination consisted of an ocular evaluation delayed skin testing sero logic testing and pulmonary radiographic evaluation

The ophthalmic examination was done in the following order (1) best cor rected visual acuity (2) external examination with hand light (3) intraocular pressure by Schiotz tonometry (4) mydriatic dilatation followed by direct and indirect funduscopy (5) description and drawing of fundus details and (6) fundus photography of scars and other abnormalities when present

At this point the definitive diagnosis of fundus scars was made e g disciform or peripheral scars of presumed ocular histoplasmosis senile disci form degeneration central serous retinopathy senile macular degeneration toxoplasmosis luetic, traumatic and other undefinable scars

For the purposes of this study a case of presumed ocular histoplasmosis disciform type was defined as an elevated hypertrophic macular or para macular scar with subretinal pigment and connective tissue proliferation This lesion was required to be associated with one or more typical atrophic peri pheral scars located anywhere in the fundus Peripheral scars were defined as round atrophic scars 2–7 disc diameters in size with pigment clumping centrally Vitreous or anterior segment inflammatory reaction could not be present

Histoplasmin skin test antigen in 1 100 dilution was obtained from Dr Lydia B Edwards* This was injected intracutaneously in a dosage of 0 1 cc in the volar surface of the right forearm and 0 1 cc of commercial intermediate strength PPD was given in the left forearm The skin tests were administered by the dental student nurse or author It was recognized that some variability must arise as result of several people administering the skin tests(96)

The tests were read by the nurse approximately 48 hours after administra tion The broadest transverse diameter of induration and erythema was measured using a millimeter gauge with the rule on the underneath surface to minimize observer bias and digit preference Prior to the onset of the study this *nurse was trained in the technique of skin test reading by participating in* several tuberculin surveys Of the 287 people examined all were tested with the histoplasmin antigen however four individuals did not return to have the skin test read (Table 3)

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* Tuberculosis Program Center for Disease Control U S Public Health Service Rockville Md

Table 3

Number and per cent of study population receiving first histoplasmin skin test and of those with less than 9 mm induration on first test who received second test

Eligible	Total	Tested	
		Number	Per cent
First test	287	283	98 6
Second test (less than 9 mm induration on first test)	146	96	65 7

Table 4

Proportion of study population for whom chest x rays were reviewed by study group

Study group	Total	Chest x rays reviewed	
		Number	Per cent
Disciform scars	19	9	47 4
Peripheral scars	15	10	66 6
Control groups	253	101	39 9
Total	287	120	41 8

Table 5

Number and per cent of study patients evaluated by uveitis expert

	Total	Examined	
		Number	Per cent
Potential cases	138	59	42 7
Office controls	84	11	13 1
Census controls	65	7	10 8
Total	287	77	26 8

Table 6

Classification of scars as evaluated by uveitis expert (Dr David Knox)

Number with scar	Scar Classification
3	Classic active disciform scar of presumed ocular histoplasmosis retina of macula or paramacular area elevated by whitish scar tissue with varying amounts of proliferated pigment epithelium in or around the scar tissue plus evidence of activity i e fresh hemorrhage or edema in area of scar plus one classic peripheral scar (depigmented atrophic with pigment present either centrally or eccentrically includes peripapillary scars also) No evidence of inflammation in the aqueous or vitreous (Figure 1)
9	Classic inactive disciform scar of presumed ocular histoplasmosis disciform scar without evidence of activity plus one classic peripheral scar (as described above) (Figure 2)
0	Highly suspect active disciform scar of presumed ocular histoplasmosis either an atypical disciform scar or absence of classic peripheral scar
3	Highly suspect inactive disciform scar of presumed ocular histoplasmosis either atypical disciform scar without activity or absence of classic peripheral scar (Figure 3)
7	Definite classic peripheral scar of presumed ocular histoplasmosis 0 3–0 7 DD irregular discrete roundish depigmented atrophic choroidal scar with a pigment clump centrally or eccentrically placed in the scar *located posterior to the equator and choroidal vessels not visible in base* of scar (Figure 4)
5	Highly suspect peripheral scar of presumed ocular histoplasmosis peripheral scar without central pigment larger than 7 DD or located anterior to the equator (Figure 5)
6	Disciform scar – not presumed ocular histoplasmosis macular or paramacular scars characterized by lipoid deposits in the subretinal space vitreous or aqueous cells peripheral scars characteristic of toxoplasmosis associated degeneration of the choroid high myopia or angioid streaks (Figure 6)
33	Peripheral scars – not presumed ocular histoplasmosis scars having hazy or ill defined borders larger than 1.5 DD in size heavily pigmented with choroidal vessels or sclera visible in base of scar presence of retinal vascular disease adjacent to scar or pigment epithelial defects (Figure 7)
11	Normal fundus examination

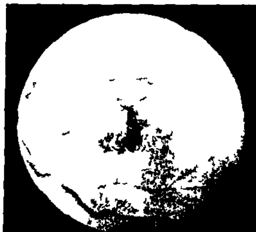


Fig 1
Classic active disciform scar of presumed ocular histoplasmosis Retina between disc and macula elevated by central focus of inflammatory reaction surrounded by signet ring proliferation of retinal pigment epithelium and an outer halo of hemorrhag

For those in whom the induration response to histoplasmin was 8 mm or less retesting was carried out on the opposite forearm The time after the first test was not constant varying from three weeks to three months the technique of administration and reading was similar to the first test Retesting was done because of the possibility that some of the older people having the peripheral or disciform scars may have lost their ability to react to the initial histoplasmin skin test because of waning sensitivity(97–99) There were 146 individuals with 8 mm or less of induration to histoplasmin on the first test of these 96 (65 7 %) were retested

Blood was drawn at the same time as the examination allowed to clot re frigerated overnight and then taken to the State Health Department Labora tories in Baltimore where it was spun down and the following tests performed (1) complement fixation tests using both yeast phase and mycelial phase *H capsulatum* antigen (2) toxoplasmosis immunofluorescent dye test and (3) cardiolipin screening test for syphilis When the cardiolipin test was positive a confirmatory fluorescent antibody test was done Complement fixation tests with toxocara canis antigen and brucellergin were done by the Center for Disease Control laboratories*

The patient was asked to indicate on the questionnaire if during the past five years full size chest x ray had been taken by the Washington County Hospital

* Emily S Chisholm Diagnostic Serology Laboratory Parasitology Section Atlanta Georgia 30333





Fig 2

Classic inactive disciform scar of presumed ocular histoplasmosis The appearance of this lesion may vary from an irregular mound of scar tissue beneath the central retina, having varying amount of pigment epithelium proliferation (left) to a small round button which gives the disciform name to the lesion (right) Around the lesion, dis turbance of pigment epithelium reflects the extent of the initial inflammatory reaction In the inactive lesion no evidence of edema or hemorrhage is present The lesion on the right may sometimes be confused with a toxocara larval granuloma except for presence of peripheral atrophic scar superior temporal to the macula



Fig 3

Highly suspect inactive disciform scar of presumed ocular histoplasmosis Disciform lesion is small and slightly yellowish in color with small surrounding disturbance of pigment epithelium Scar superior to macula is too small to be characteristic



Fig 1

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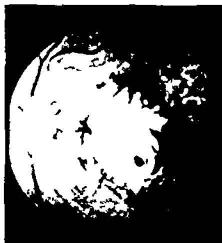


Fig 6

Disciform scar – not presumed ocular histoplasmosis The presence of large amounts of pigment tissue differentiates this scar from that found in histoplasmosis The scar tissue has a dirty yellow appearance





Fig 7

Peripheral scars – not presumed ocular histoplasmosis The presence of a dirty grey tissue in the base of the scar on the left, plus the venous sheathing would distinguish this scar from histoplasmosis In the scars on the right, the large solid mass of pigment tissue in the base is not found in the classic peripheral scar

Table 7
Agreement of uveitis expert and author in selection of cases and non cases

Classification by uveitis expert	Classification by author		Total
	Fundus compatible with presumed ocular histoplasmosis	Fundus not compatible with presumed ocular histoplasmosis	
Fundus compatible with presumed ocular histoplasmosis	20	7	27
Fundus not compatible with presumed ocular histoplasmosis	5	45	50
Total	25	52	77

Agreement $\frac{65}{77} = 84.4\,\%$

Radiology Department or 10 mm photofluorographs by the Washington County Tuberculosis Association Those films were reviewed by Dr George W Comstock and classified as to the presence of calcified pulmonary nodules consistent with systemic histoplasmosis Results of the eye examination were not known by the reader at the time of the x ray review Only 41 8 % of those participating in the study had chest x ray taken within the past 5 years that could be located (Table 4)

Expert s Evaluation

A subgroup of the patients examined who had disciform scars of any kind peripheral scars suggestive of presumed ocular histoplasmosis central serous retinopathy and a few normal subjects were then reviewed by Dr David Knox of the Wilmer Ophthalmologic Institute He has had over ten years experience in the field of uveitis and has particular knowledge of the ocular

Table 8

Derivation of cases of disciform and peripheral scars used in study

	Cases of Presumed ocular histoplasmosis		
	Disciform	Peripheral	Total
Cases diagnosed by uveitis expert	15	12	2
Cases added by author	4	3	[illegible]
Total	19	15	34

picture under investigation This selected subgroup was examined on two days one week apart at the Johns Hopkins Training Center for Public Health Research in Hagerstown The examination at this time consisted of visual acuity determination slit lamp biomicroscopy and dilated funduscopic examination Seventy seven people were examined by this uveitis expert (Table 5) These patients were examined without knowledge of the results of the histo plasmin skin test or the results of the ocular evaluation by the author The classification of scarring used by the uveitis expert is given in Table 6 and examples are given in Figures 1–7

Seven cases of disciform or peripheral scars designated by the author as compatible with presumed ocular histoplasmosis were not seen by the uveitis expert Since the overall agreement of the expert and the author was 84 4 % (Table 7) and since the number of total cases both definite and highly suspect was small it was decided to include these additional seven cases in analyzing variables that might be associated with the disease (Table 8) For the purposes of analysis the definite and highly suspect cases were grouped as a unit

Nineteen people were identified by the study as having central disciform scars either characteristic or highly suggestive of presumed ocular histoplasmosis and 15 people identified as having peripheral scars Ten of the individuals with peripheral scars came from the group of potential cases whereas two people came from the office controls and three were from the census controls This gave a prevalence for the peripheral scars of 2 4/100 among the office and 4 6/100 among the census controls (Table 9) This prevalence is similar to the 2 4 % found by Smith & Ganley(52) and the 1 6 % found by Asbury(50) Because of the small number of people with peripheral scars the 5 cases from the control groups were included with the 10 individuals from the potential case group for the purpose of examining their characteristics these 5 individuals are also included with their respective control groups for comparison with the cases having disciform macular scars

The age distribution of people with disciform and peripheral scars was limited to the 30–69 year age range while 12 3 % of the control groups were 70 years of age and older (Table 10) In order to keep the study groups comparable the controls were limited to the same age range as the cases for subsequent data analysis

Table 9

Prevalence of people with peripheral scars among office and census controls

	Total in group	People with peripheral scars	
		Number	Prevalence per 100
Office controls	84	2	2 4
Census controls	65	3	4 6
Total	149	5	3 4

Table 10

Selected demographic and social characteristics of cases and controls from 1970 study questionnaire (total population)

Characteristics	Cases		Controls		
	Disciform	Peripheral	Scar	Office	Census
Number of persons	19	15	109	84	65
Age 30–69 years (%)	100 0	100 0	85 3	86 9	87 7
White race (%)	100 0	100 0	99 1	98 8	100 0
Male sex (%)	42 1	60 0	52 3	40 0	50 1
Urban residence (%)	63 1	53 3	46 8	48 8	40 0
Married (%)	94	86 6	78 9	81 0	81 5
Median education (grade)	10 6	11 9	12 1	12 2	12 1

Table 11 lists selected demographic and social characteristics of the disciform and peripheral cases and the control groups The cases and controls were reasonably similar in median age race and marital status A larger percentage of the disciform cases were female (57 9 %) as compared to the peripheral scars (40 %) and the control groups (51 1 %) This should be contrasted with previous studies which show a greater male frequency(24–26 29) The sex distribution of the disciform cases was similar to that of the office controls (56 2 % female) Patients with disciform scars had slightly less education (10 6 grades) as compared to the controls (12 3 years) Fewer people with disciform (43 7 %) and peripheral (45 4 %) scars attended church at least once a month than controls (61 7 %) *These differences were not significant when tested by* chi square analysis corrected for continuity (Table 12) or by partitioned chi square(100) (Table 13) There were no statistically significant differences among the control groups on any of the factors tested for this reason the three control groups were pooled for comparison with the disciform cases by significance tests

Residency characteristics of the study populations are considered in Table 14 People with disciform scars tended to come from an urban area (63 1 %)

Table 11

Selected demographic and social characteristics of cases and controls from 1970 study questionnaire (age 30–69 years) and from 1963 Washington County census data (age 23 5–59 years)

Characteristics	1970 questionnaire data					
	Cases		Controls			
	Disciform	Peripheral	Total	Scar	Office	Census
Number of persons	19	15	223	93	73	57
Median age (years)	49 0	49 0	49 9	50 3	51 3	45.5
White race (%)	100 0	100 0	99 1	98 8	98 6	100 0
Male sex (%)	42 1	60 0	48 9	51 6	43 8	50 9
Married (%)	94 7	86 6	85 7	83 9	86 3	87 7
Median education (grades)	10 6	11 9	12 3	12 3	12.3	12 2
	1963 census data					
Age 23 5–59 years in 1963 and present in census (%)	94 7	73 3	89 6	87 1	89 0	94 7
Church attendance one or more times per month (%)	43 7	45 4	61 7	60 5	66 1	58 4

whereas only 41 7 % of the controls lived in the city 53 3 % of people with peripheral scars lived in the same area Although there were no differences in the per cent of time lived in Washington County between those with disciform scars (52 6 %) and the controls (54 2 %) more cases spent at least 90 % of their life in an urban environment (42 1 %) as compared to the controls (22 9 %) This agrees with the finding that most people with disciform scars had never lived on a farm (78 9 %) or in the suburbs (84 2 %) the per cent of cases having lived in rural non farm areas is quite similar to the controls

The 1963 Washington County census listed many housing characteristics

Table 1?

Relative risk and chi square significance results(100) for disciform scars compared to pooled controls and chi square significance results among the three control groups for each characteristic

Characteristics	Disciform scars		Control groups
	Relative risk	χ (1 df)†	χ (2 df)
Histoplasmin positive		10 043*	4 ,81
Never lived in suburb	4 30	4 861*	2.342
Frequent exposure to birds	3 43	3 600	1 430
Tuberculin positive	3 ?9	4 4,3**	9048
House of wood frame construction	3 26	4.571 *	2 491
75 % of week indoors	3 04	3 130	2 058
Yeast C F 1 8 dilution or greater	2 83	1.983	
Smoked 25 or more cig /day	? 80	3 237	2.213
Single bathroom	2 75	1 840	891
Exposure to dust	2 51	2 489	
Urban living 90 % of life	2 45	2 54,	8?9

† corrected for continuity
* significant at 05 level

several of which are given in Table 15 The most striking characteristic was the number of disciform cases who lived in a wood frame house in 1963 (44 4 %) as compared to the controls (19 7 %) The age of house absence of concrete cellar use of coal for fuel house heated by hot air register and presence of only one bathroom in the house although showing some differences between the disciform cases and the controls were not at a statistically significant level

Table 13

Relative risk and partitioned chi square(100) for disciform scars compared to pooled *controls on selected characteristics*

Characteristics	Disciform scars		Total
	Relative risk	χ^2 (1 df)	χ (4 df)
Frequent exposure to birds	3 43	5 268**	6 [illegible]26
Smoked 25 or more cig/day	2 80	4 408**	6 49[illegible]
75 % or more of week indoors	3 04	4 034**	6 066
Urban living 90 % of life	2 45	3 503	4 346
Frequent exposure to dust	2 51	3 438	1 251
Urban residence	2 40	3 206	5 175

** significant at 05 level

The disciform cases also had greater tendency to spend 75 % or more of their time at work (78 9 %) and 75 % or more of their total week (78 9 %) in doors 84 2 % of disciform cases also tended to have jobs that could be clas sified as indoor work Fewer controls spent 75 % or more of their time at work indoors (61 4 %) or 75 % or more of their week indoors (55 2 %) or have what might be considered an indoor occupation (75 3 %) People with peripheral scars were much like the controls in their work characteristics (Table 16) The disciform group tended to more frequently come in contact with dust around the house or in their occupations (36 8 %) than did the control groups (18 8 %) there was no difference in their exposure to fumes and solvents

Although more cases had frequent contact with birds (26 3 %) than controls *(8 1 %) as seen in Table 17 there was no difference in exposure to chickens* pigeons starlings bats guano birds roosting around the house or having cleaned chicken houses Hagerstown until very recently had been inundated by large flocks of starlings that roosted on the downtown buildings There was ample opportunity for these urban inhabitants to be exposed to bird guano

Table 14
Residency characteristics of cases and controls from 1970 study questionnaire (age 30–69 years)

Characteristics	Cases		Controls			
	Disciform	Peripheral	Scar	Total	Office	Census
Number of persons	19	15	273	93	73	5
Urban residence (%)	63.1	53.3	41.7	40.9	46.6	36.8
90 % or more of life spent in Washington County (%)	52.6	66.6	54.2	57.0	49.3	56.1
90 % or more of life spent in urban area (%)	42.1	26.7	22.9	27.6	26.0	19.3
Never lived on farm (%)	8.9	66.6	66.4	64.5	6 1	68.4
Never lived in suburb (%)	84.7	53.3	53.3	48.4	56.2	57.9

** statistically significant at .05 level

particularly those who worked in the large factories and warehouses where the guano was heavily concentrated. Pigeon racing was also a popular sport in this area and several people in the study had raised pigeons for this purpose.

Table 18 lists several illnesses compatible with benign pulmonary histoplasmosis to determine whether individuals with the disciform scars might have had more severe infections with *H. capsulatum* than the rest of the population. There were no differences in the past history of the cases and controls with respect to prolonged colds, influenza, pleurisy or pneumonia. A slightly higher frequency of allergies among people with disciform scars (73.7 %) as compared to the controls (59.7 %) was found. Allergic reactions to medication were present in 6 out of the 8 male cases and in 8 of the total 19 cases. Sinusitis was the second most frequent type of allergy among the cases (6).

People with disciform scars did not differ from the controls in the proportion smoking at the time of the examination (42.1 % vs. 40.8 %) or having ever

Table 15

Selected housing characteristics of cases and controls obtained from 1963 Washington County Census data (age 23.5–59 years)

Characteristics	Cases		Controls			
	Disciform	Peripheral	Total	Scar	Office	Census
Number	18	11	169	71	53	34
House built between 1900–1958 (%)	87.5	100 0	69 6	66 6	67 7	73 6
Wood frame construction (%)	44 4	9 2	19 7**	19 7	14 3	25 9
Cellar not concrete (%)	33 3	36 4	21 6	22 3	21 9	20 4
Coal fuel (%)	38 9	27.3	23 5	25 9	21.5	22.2
Air furnace heat (%)	61 1	54 5	50 0	45 6	53 8	51 9
Single bathroom (%)	83 5	81 8	64 5	66 6	66 1	59 2

** significant at 05 level

smoked (63 2 % vs 59 2 %) (Table 19) However people with disciform scars did tend to be heavier smokers 36 8 % having smoked 25 or more cigarettes a day This can be contrasted with the 17 5 % heavy cigarette (or cigarette equivalent) consumption by the controls This same frequency of heavy smoking persists after age and sex adjustment (Table 20) The cases tended to smoke cigarettes exclusively and to inhale the smoke deeply Of those that stopped smoking all of the cases did so within the preceding 10 years while only 65 9 % of the controls stopped within this same period

Age and sex differences in smoking history among the total study population are given in Table 21 more males (76.5 %) smoked than females (39 0 %) among women smoking frequency declined with increasing age In Table 22 age and sex adjusted mean induration to histoplasmin for non smokers (8 53 mm) is compared to those who smoked 1–14 cigarettes per day (6 82 mm) or 15 or more cigarettes per day (9 47 mm) There was only 0 94 mm of induration difference between the non smokers and heavy smokers Light smokers had less

Table 16

Comparison of occupation and occupational exposure among cases and controls from 1970 study questionnaire (age 30–69 years)

Characteristics	Cases		Controls			
	Disciform	Peripheral	Total	Scar	Office	Census
Number of persons	19	15	223	93	3	5
75 % or more of work indoors (%)	78 9	60 0	61 4	55 9	67 1	63 2
75 % or more of week indoors (%)	78 9	60 0	55 2*	50 5	61 6	54 4
Indoor occupation (%)	84 2	53 3	75 3	4 1	74 0	78 9
Exposure to fumes and solvents (%)	73 7	80 0	74 0	71	77 8	71 4
Frequent exposure to dust (%)	36 8	20 0	18 8	16 2	16 4	26 3

* significant at 05 level

induration than either group There was also no association between the amount smoked and histoplasmin sensitivity (Table 23)

The frequency distribution of reactions to the histoplasmin skin test is given in Table 24 There was no clear antimodal separation of the positives and negatives and a flattened distribution of those who were sensitive to the anti gen. This plus the fact that there was a large number of hematomas produced by the skin test which caused a small false positive induration made it desirable to use the conventional 5 mm of induration definition of a positive reactor All the disciform cases had 5 mm or more of induration while only 60 % of the people with peripheral scars and only 60 7 % of the controls had a positive histoplasmin skin test (Table 25) A similar association was found with cases diagnosed by the uveitis expert (Table 26) This association of a positive histoplasmin skin test and disciform macular scarring was significant at the 01 level Of those given a repeat histoplasmin skin test age 30–69 years 83 3 % of people with peripheral scars who had less than 5 mm of indu

Table 15

Selected housing characteristics of cases and controls obtained from 1968 Washington County Census data (age 23.5–59 years)

Characteristics	Cases		Controls			
	Disciform	Peripheral	Total	Scar	Office	Census
Number	18	11	169	71	58	34
House built between 1900–1958 (%)	87.5	100 0	69 6	66 6	67 7	73 6
Wood frame construction (%)	44 4	9 2	19 7**	19 7	14 3	25 9
Cellar not concrete (%)	33 3	36 4	21 6	22 3	21 9	20 4
Coal fuel (%)	38 9	27 3	23 5	25 9	21 5	27 [illegible]
Air furnace heat (%)	61 1	54 5	50 0	45 6	53 8	51.9
Single bathroom (%)	83 5	81 8	64 5	66 6	66 1	59 2

** significant at 05 level

smoked (63 2 % vs 59 2 %) (Table 19) However people with disciform scars did tend to be heavier smokers 36 8 % having smoked 25 or more cigarettes a day This can be contrasted with the 17 5 % heavy cigarette (or cigarette equivalent) consumption by the controls This same frequency of heavy smoking persists after age and sex adjustment (Table 20) The cases tended to smoke cigarettes exclusively and to inhale the smoke deeply Of those that stopped smoking all of the cases did so within the preceding 10 years while only 65 9 % of the controls stopped within this same period

Age and sex differences in smoking history among the total study population are given in Table 21 more males (76 5 %) smoked than females (39 0 %) among women smoking frequency declined with increasing age In Table 22 age and sex adjusted mean induration to histoplasmin for non smokers (8 53 mm) is compared to those who smoked 1–14 cigarettes per day (6 82 mm) or 15 or more cigarettes per day (9 47 mm) There was only 0 94 mm of induration difference between the non smokers and heavy smokers Light smokers had less

Table 19

Smoking history of cases and controls on 19 0 study questionnaire (age 30-69 years)

Characteristic	Cases		Controls			
	Disciform	Peripheral	Total	Scar	Office	Census
Number of persons	19	15	223	93	73	5
Smoked ever	63 2	80 0	59.2	55 9	61	61 4
Smoke now	42 1	33 3	40 8	36 5	3 0	5 6
Smoke 25 or more cigarettes per day	36 8	20 0	17 5**	19 3	19 4	10 0
10 or less years since stopped smoking	100 0	37 5	65 9	61 1	66 6	80 0
Inhale deeply (among those who smoke)	37 5	50 0	25 3	26 5	29 6	20 0
Smoke cigarettes only (among those who smoke)	100 0	87 5	7 8	80 6	75 9	76 2
Median age first smoked	18 4	18 6	18 9	18 7	19 9	18 8

* significant at 05 level

Table 20

Age and sex adjusted cigarette consumption per day of people with disciform scars compared to grouped controls of same age (age 30–69 years)

	Total	Non smoker		1–24 cigarettes		25 or more cigarettes	
		Number	Per cent	Number	Per cent	Number	Per cent
Cases (age and sex adjusted to controls)	221	91	41 2	92	41 6	95 1	43 0
Controls	221	71 2	32 2	54 7	24 8	38	17 2

Table 21

Mean histoplasmin induration for total study population by cigarette consumption

Age	Total number	*Male* Mean histoplasmin induration (mm)				Per cent ever smoked
		Total	Non smoker	1–14 cig	15+ cig	
30–49	59	11 98	14 55 (9)*	8 90 (11)*	11 20 (39)*	83 1
50–69	58	10 34	8 72 (18)	9 66 (6)	11 32 (34)	69 0
70+	15	4 86	4 66 (3)	4 50 (8)	5 75 (4)	80 0
Total	132	10 14	10 06 (30)	7 68 (25)	10 90 (77)	76 5
Female						
30–49	71	8 16	7 16 (36)	7 64 (14)	10 23 (21)	50 0
50–69	59	6 66	6 76 (38)	5 22 (9)	7 41 (12)	35 6
0+	20	5 10	5 61 (18)	0 50 (2)	(0)	10 0
Total	150	7 16	6 69 (92)	6 20 (22)	9 21 (33)	39 0

* parentheses contain number in each class

Table 2?

Mean age and sex adjusted histoplasmin induration for total study population by cigarette consumption (for those with induration)

	Mean histoplasmin induration (mm)			
	Total	Non smokers	1–14 cigarettes per day	15 or more cigarettes per day
Male (age adjusted)	136	10 62	8 5	10 55
Female (age adjusted)	151	6 64	[illegible]	8 49
Age and sex adjusted	937	8 53	6 89	9 47

ration on the first test converted to 5 or more millimeters on the retest whereas only 23 2 % of the controls on retest gave a positive response (Table 27) These figures applied to their respective groups (Table 28) gave an estimated 93 3 % histoplasmin positivity to the people with peripheral scars and 69 5 % positively to the controls

The disciform cases had larger median induration (14 5 mm) than those with peripheral scars (8 5 mm) or controls (9 1 mm) Complement fixing anti bodies using yeast phase antigen were positive at 1 8 dilution in 38 9 % of disciform cases and 21 4 % of controls mycelial phase C F reactions were positive at 1 4 dilution in 11 1 % of disciform cases and 3 2 % of the controls Tuberculin sensitivity at 10 mm of induration was also greater for people with the disciform scars (36 8 %) as compared to the controls (15 1 %) No dif ference in reactivity to the toxoplasmosis immunofluorescent dye test was found There were no reactors to the toxocara or brucella C F tests and only four reactors among the controls to the immunofluorescent test for syphilis

In chest x rays from people participating in the study calcification was found in 44 4 % of the cases and in only 26 7 % of the controls (Table 29) Thirty per cent of those with peripheral scars had pulmonary calcification con sistent with histoplasmosis There was no evidence from this study that indi viduals with pulmonary calcification had greater reactivity to histoplasmin than did those without such calcification (Table 30)

A survey of high school students by Comstock et al in 1969(77) established areas of varying histoplasmin sensitivity in Washington County The residen

Table 21

Mean histoplasmin induration for total study population by cigarette consumption

Age	Total number	*Male* Mean histoplasmin induration (mm)				Per cent ever smoked
		Total	Non smoker	1–14 cig	15+ cig	
30–49	59	11 28	14 55 (9)*	8 90 (11)*	11 90 (39)*	83 1
50–69	58	10 34	9 72 (18)	9 66 (6)	11 32 (34)	69 0
70+	15	4 86	4 66 (3)	4 50 (8)	5 75 (4)	80 0
Total	132	10 14	10 06 (30)	7 68 (25)	10 90 (77)	76 5
			Female			
30–49	71	8 16	7 16 (36)	7 64 (14)	10 23 (21)	50 0
50–69	59	6 66	6 76 (38)	5 22 (9)	7 41 (12)	35 6
70+	20	5 10	5 61 (18)	0 50 (2)	(0)	10 0
Total	150	7 16	6 69 (92)	6 20 (25)	9 21 (33)	39 0

* parentheses contain number in each class

Table 24

Frequency distribution of sensitivity to histoplasmin and tuberculin from total tested population

Frequency groups (mm)	Histoplasmin		Tuberculin	
	Number in group	Per cent distribution	Number in group	Per cent distribution
0– 2	69	24.2	176	62.2
3– 5	56	19.6	47	16.6
6– 8	22	7.7	6	2.1
9–11	36	12.6	18	6.4
12–14	35	12.3	16	5
15–17	37	13.0	9	3.2
18–20	16	5.6	5	1.8
21–23	7	2.5	0	0
24–26	5	1.8	1	0.4
27–29	0	0	0	0
30–32	0	0	3	1.1
33+	2	0.7	2	0.8
Total	285	100.0	283	100.0

cies of cases and controls in 1963 were compared to the histoplasmin sensitivity for their area (Table 31) Hagerstown although having a lower range of prevalence to histoplasmin (0–67 %) than the rest of the County (0–100 %) had a higher frequency of people with peripheral scars (5.5) as compared to the rest of the county (4.4) Although there was no relationship between prevalence of disciform cases and frequency of histoplasmin sensitivity there was a slight tendency for the frequency of people with peripheral scars to increase as the prevalence of histoplasmin sensitivity increased

Table 23

Comparison of smoking habits and histoplasmin sensitivity of total tested population by sex

	Male			Female		
	Number in group	Number with 1 mm or more of induration	Per cent with induration	Number in group	Number with 1 mm or more of induration	Per cent with induration
Non smoker	30	26	86 7	92	79	85 9
Smoked ever						
1–14 cig	25	23	92 0	25	20	80 0
15+ cig	78	62	79 5	33	29	87 9
Total	133	111	83 4	150	128	85 3

Table 27

Repeat histoplasmin skin test by sex for patients with peripheral scars and controls individuals with ≤ 4 mm induration on first test who converted to ≥ 5 mm induration on second test (age 30–69)

	Number with ≤ 4 mm	Retested		Converted to ≥ 5 mm induration	
		Number	Per cent	Number	Per cent
Peripheral scars					
male	2	2	100 0	2	100 0
female	4	4	100 0	3	75 0
Total	6	6	100 0	5	83 3
Controls					
male	28	18	64 3	7	38 8
female	57	38	66 6	6	15 8
Total	85	56	65 9	13	23 [illegible]

Table 28

Comparison of histoplasmin sensitivity of people with peripheral scars and controls based on results of original and repeat histoplasmin skin tests (age 30–69 years)

	First test			Second test		Estimated total individuals on both tests with ≥ 5 mm induration	
	Number in group	≤ 5 mm induration		Conversion rate	Estimated total converters	Number	Per cent
		Number	Per cent				
Peripheral scars	15	6	40 0	83.3 %	5	14	93.3
Controls	215	85	39 7	23 2 %	19 7	148 7	69.5

This study offers additional confirmatory evidence for the etiologic association of infection with *H capsulatum* and disciform macular scars of presumed ocular histoplasmosis The association was tested by three measures of histo plasmosis infection – histoplasmin skin test sensitivity and induration C F reaction and pulmonary calcification all were consistent with exposure and infection with *H capsulatum*

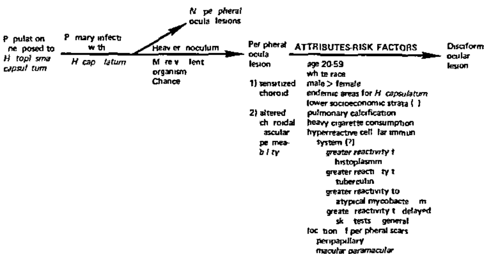
Peripheral scar cases were unlike those with disciform scars with respect to indices of histoplasmosis infection or any other attributes Analysis of the age specific prevalence rates for people with peripheral scars from Walkersville (70) showed no increase with age suggesting that the peripheral lesions oc curred during the primary systemic infection and that occurrence resulting from reinfection must be rare Woods & Wahlen(10 11) pointed out that these peripheral lesions were atrophic at the time of onset of the disciform process and must therefore have occurred at an earlier period Recent confirmatory rabbit experiments by Wong & Green(64) showed that intravenous injection of organisms after immunity had developed also failed to produce ocular in flammation The presence of pulmonary calcification in 50 % of the disciform cases also suggests that primary infection must have taken place from 2 months to 6 years previously(101) but more likely had occurred in childhood(102)

In Washington County 54 % of the population sample had been sensitized to *H capsulatum* by high school age in some areas the prevalence had ranged to over 90 %(95) Presumably individuals with peripheral scars were exposed at a similar age The attributes of people with peripheral scars should be similar to those attributes of the general population previously exposed to the organism except that those with eye lesions may have received a more virulent strain or larger inoculum of *H capsulatum* during the primary infection (63 103 104)

Waning of skin test sensitivity is known to occur with time after exposure in both human(97 98) and animal infections(99) It is to be expected that there should be some waning of sensitivity among people with peripheral scars if these people were infected when they were young This waning of sensitivity may explain why Asbury(65) found positive histoplasmin skin tests in only 63 % of his cases with peripheral scars although all of his skin test negative cases had pulmonary calcification Because the cellular immune system in

Table 3[9]

Attributes and risk factors related to the development of disciform macular lesions in presumed ocular histoplasmosis



nonreactive sensitized individuals may be boosted by the first histoplasmin skin test to respond to the repeat test(97) the greater response of people with peripheral scars on the second skin test as compared to the controls is further evidence for the etiologic association with *H capsulatum*

Although it was necessary in this study for peripheral atrophic scars to be present for the diagnosis of presumed ocular histoplasmosis no typical disci form cases were found in the present study who did not have one or more peripheral atrophic scars present *This is true also of the experience of* Knox (67) who has only seen a rare disciform lesion without these associated scars

The modal age of onset of the disciform scars is in the fourth decade(25 29) whereas the age of primary exposure to the organism and presumably the production of the peripheral process is in the second decade of life Since the evidence suggests that disciform lesions arise in patients who have peripheral scars it may be inferred that the interval between the onset of the peripheral lesion and the disciform process ranges between 10 and 30 years People with *peripheral scars probably represent a reservoir from which cases of disciform* lesions arise

Some of the characteristics of people with disciform scars may be similar to those with peripheral scars because the former is a subgroup of the latter But considering the long interval between primary infection and onset of the disciform lesion they may also differ in many respects

Three hypotheses have been proposed to explain the development of disci

Table 33

Summary of postulated interrelationships of risk factors and attributes concerned with the development of disciform macular lesions in systemic histoplasmosis

A Previous ocular dissemination
  1) sensitized choroid (peripheral atrophic scar)
    - persistence of viable *H capsulatum* cells (doubtful)
    - remaining fragments of *H capsulatum* cells
    - tissue fixed antigen
    - sensitized lymphocytes and plasma cells in bed of atrophic scar
  2) altered choroidal vascular permeability
    - results from initial ocular seeding
    - remains sensitive to noxious stimuli for long periods of time
    - allows interaction of primed cellular immune elements and antigen when stressed
    - may be sensitive to agents that increase systemic blood pressure e g nicotine excess thyroid hormone pregnancy etc

B Heavy cigarette consumption
  - indirectly induces congestion of choroidal vascular system in individuals reactive to nicotine - possibly stresses sensitized choroidal vascular system

C Hyperreactive cellular immune system
  - innate characteristic (?)
  - Freund s adjuvant effect from previous exposure to mycobacterium (?)

D Hyperreactivity to histoplasmin
  - innately hyperreactive cellular immune system (?)
  - continued re exposure to *H capsulatum* (live in endemic area)
  - Freund s adjuvant effect (?)

E Location of peripheral scars
  1) peripapillary
    - not understood found in 85 % of individuals with disciform lesions
  2) macular paramacular
    sensitive to focal accumulation of subretinal and intraretinal inflammatory products
    - high pressure high volume choroidal vascular supply

F Pulmonary calcification
  - young age at original infection
  - innate hypersensitivity (?)
  - *Freunds adjuvant effect (?)*

G Age 20-39 years
  - age of greatest re exposure to organism
  - age of greatest reactivity to histoplasmin
  - age of great reactivity to delayed skin tests in general

H White race
  - not understood

I Male > Female
  - male has greater opportunity for re exposure
  - male has greater response to histoplasmin

form lesions in patients with peripheral scars One theory is that *H capsulatum* cells remain in symbiosis with choroidal tissue and become reactivated under stress or when antibodies have waned However inability to demonstrate yeast cells in animal models approximately 2 months after infection(61 64) would not support this contention A second hypothesis suggests that there might be secondary infection with reseeding of the retina Although Krill et al (30) have observed a new inflammatory focus in the presence of atrophic scars it does not seem reasonable that repeat ocular dissemination causes the disciform lesion because evidence of acute disease is absent from other areas of the fundus The fact that 25 % of the cases tend to be bilateral with the second eye becoming involved months to years after the first also argues against the reinfection hypothesis Wong & Green(64) were not able to produce ocular lesions once immunity had been acquired by their animals The third hypothesis originally proposed by Woods & Wahlen(10 11) was that the disciform disease represents a hypersensitivity reaction to histoplasmin This hypothesis still seems the most tenable In the second eye of several patients having the disciform scar in the first eye the process has been observed to begin around an old peripheral atrophic scar contiguous to the macula(33 34 67)

It might be postulated that the original ocular infection in some way sen sitizes *the choroid in the area of the atrophic scar or that the antigen becomes* tissue fixed and therefore primed for attack by the cellular immune system Salfelder & Sethi have observed yeast cell debris remaining in the area of the peripheral scar after experimental ocular infection(62) The macular area differs from the rest of the posterior eye in being served by a rich high pres sure vascular plexus(105) it is extremely sensitive to accumulation of tissue fluid Atrophic fundus scars away from the macula may well have the same antigenic characteristics as those near the fovea but the retina and choroid elsewhere lack the capacity to accommodate focal sub retinal accumulation of edema hemorrhage or inflammatory cells Hyvarinen et al (32) have docu mented a flare up of one of these atrophic scars by fluorescein angiography

The presence of a greater induration response to histoplasmin in individuals with disciform scars as compared with those who have peripheral scars or the controls is consistent with the hypersensitivity hypotheses Lymphoblastic transformation studies suggest that skin sensitivity reflects quantitatively and qualitatively the status of the cellular immune system(106–109)

Presence of larger induration in these cases might be accounted for by heightened innate allergic tendencies in the individual Weber et al (73 74) have found these cases more reactive to delayed skin tests in general than were their patients with other types of uveitis It has also been suggested that the increased induration might result in part from seepage of antigen from yeast cells in encapsulated pulmonary nodules this seepage has been responsible for enlargement and calcification of the histoplasmoma(110 11) Calcified

nodules occur in 50–80 % of people with the disciform process(38 40) However this study finds no evidence that people with pulmonary calcification have greater induration than those without such calcification

Another source of heightened induration might be the result of continued re exposure to or reinfection with *H capsulatum* Pulmonary reinfection can occur even in the presence of known immunity(112 115) particularly if the inoculum is large(113) or if reinfection is from heterologous strains(114–115) Reexposure to and reinfection with the organism may be entirely asymptomatic (112) In areas where histoplasmin sensitivity is prevalent it has been postulated that reexposure to *H capsulatum* produces the high levels of induration found in the third to sixth decades(70) Complement fixing antibodies have approximately a 2–3 year half life after chronic histoplasmosis but may range occasionally as long as 9 years(116) Reexposure to the organism could account for the high frequency of complement fixing reactors among the control groups It has been shown that injection of small amounts of antigen as used in the histoplasmin skin test may stimulate both the serologic(78 117) and the cellular immune system(97)

Onset of the disciform scars occurs during the age when histoplasmin induration is largest in the general population In the older ages there is both waning(97) and impairment of delayed hypersensitivity(118) The disciform process is also more frequent among men than women and men tend as a group to have larger induration than women men are felt to have more opportunity for contact with the organism(71)

This study suggests that people who live and work indoors have greater opportunity for developing the disease than those who live out of doors or on a farm Although birds do not roost in or around the houses of cases to any greater extent than around the houses of people with peripheral scars or controls the cases did come in more frequent contact with birds bats and their guano than did the controls Wood frame houses built during the first half of this century in Hagerstown with their open air registers and dirt cellars would be likely to harbor bird and bat roosts under the eaves and within the partitions The open furnace register is an effective disseminatior of house dust

The high association of positive tuberculin skin tests with the disciform disease was unexpected It was thought that tuberculin sensitivity might act as an internal control with equal frequency among cases and controls It is not known whether this greater prevalence of tuberculin sensitivity is related to an overall heightened cellular immune system(73 74) or whether it may be related to the socioeconomic strata to which the disciform cases belong Kuemmerer & Comstock(119) have shown that among high school students in Washington County larger reactions to tuberculin occurred among urban residents and those who ranked lower on the socioeconomic scale whose parents both smoked had less education and went to church less frequently Many of

these characteristics apply to those individuals with disciform scars in the present study predominately urban less educated heavy smokers and less religious

The observation of heavy smoking among cases of disciform disease was made by Knox(67) while examining the smoking habits of people with different types of uveitis The finding of heavy smoking among the cases is confirmed by this study Smoking is known to cause an irritative effect on the tracheobronchial tree(120) this conceivably could provide a milieu in which a greater inflammatory response and therefore a heightened cellular immune reaction might occur However age and sex adjusted mean induration did not show any association with the amount of cigarettes smoked nor was there an association of greater histoplasmin sensitivity with the number of cigarettes consumed

The choroidal vascular bed at lower levels of intraocular pressure has no autoregulatory mechanism and may develop passive congestion in the presence of systemic nicotine(121) and other peripheral vasoconstrictors(122) Once the choroidal vascular system has been altered by previous inflammation it remain more permeable than normal choroid this phenomenon has been postulated as one mechanism for the production of recurrent anterior uveitis(123 124) It is likely that choroidal vessels in the area of the peripheral atrophic scars likewise have a lowered permeability threshold It may be that either nicotine or other tobacco products by increasing the congestion of the choroid stresses the abnormal blood choroidal barrier to allow interaction of the primed cellular immune system and persistent antigen or sensitized tissue in the atrophic scars

It may also be possible that circulating *H capsulatum* antigen or antigen antibody complexes pass through these congested and abnormally permeable choroidal vessels into the region of a peripheral atrophic scar Wong & Green (64) in their animal model have shown that plasma cells and lymphocytes persist at the site of these atrophic lesions long after the initial granulomatous process has resolved These immune cells presumably highly sensitive to the antigen may then respond by producing a focal inflammatory reaction

If this process happens to localize in an atrophic scar in the region of the macula or optic nerve a disciform lesion might ensue if the antigen deposits in a scar elsewhere in the fundus an asymptomatic enlargement of the lesion or leakage of fluorescein may be all that is noticed

In summary this study has shown a strong association of positive histoplasmin skin tests and the disciform scars of presumed ocular histoplasmosis This process seems to occur in those patients whose macular choroid has been previously sensitized in the presence of heightened cellular immune response to histoplasmin and possibly requires an altered choroidal vascular permeability The heightened immune response may be stimulated by reexposure to the organism or result from an intrinsic hypersensitive allergic system The

choroidal vascular permeability may be indirectly altered by heavy cigarette consumption

The postulated risk factors involved in the development of the disciform lesions from infection with histoplasmosis are

(1) primary infection with *H capsulatum* (2) development of initial choroidal lesions in the macular and paramacular areas (3) maintenance of heightened reactivity to histoplasmin antigen i e from reexposure to *H capsulatum* from exposure to other stimulants of the cellular immune system (e g tuberculosis) or because of innate hyperreactivity and (4) agents which stimulate choroidal vessel permeability (Tables 32 and 33)

1 Darling S T A protozoan general infection producing pseudotubercles in the lungs and focal necrosis in the liver spleen, and lymph nodes *J A M A 46* 1283–1285 (April 28) 1906

2 Reid J D Scherer J H Herbut P A & Irving H Systemic histoplasmosis diagnosed before death and produced experimentally in guinea pigs *J Lab Clin Med 27* 419–434 (Jan) 1942

3 Palmer C E Nontuberculus pulmonary calcifications and sensitivity to histoplasmin *Public Health Rep 60* 513 (May) 1945

4 Christie A & Peterson J C Pulmonary calcification in negative reactors to tuberculin *Amer J Public Health 35* 1131–114 (Nov) 1945

5 Day R Experimental ocular histoplasmosis *Amer J Ophthal 32* 1317–1336 (Oct) 1949

6 Krause A C & Hopkins W G Ocular manifestations of histoplasmosis *Amer J Ophthal 34* 564–566 (April) 1951

7 Woods A C Jacobs L Wood R M & Cook M K A study of the role of toxoplasmosis in adult chorioretinitis *Amer J Ophthal 3* 163–177 (Feb) 1954

8 Woods A C *Endogenous uveitis Baltimore* Williams and Wilkins 1956

9 Schlaegel T F Granulomatous uveitis An etiologic survey of 100 cases *Trans Amer Acad Ophthal and Otolaryn 6[illegible]* 813–825 1958

10 Woods A C & Wahlen H E The probable role of benign histoplasmosis in the etiology of granulomatous uveitis *Trans Amer Ophthal Soc 57* 318–343 (May) 1959

11 Woods A C & Wahlen H E The probable role of benign histoplasmosis in the etiology of granulomatous uveitis *Amer J Ophthal 49* 205–220 (Feb) 1960

12 Junius P & Kuhnt H *Die Scheibenformige Entartung der Netzhautmitte* Berlin, S Karger 1926 Vol 7

13 Kahler A R & O Brien C S Disciform degeneration of the macula *Arch Ophthal 13* 937–959 (June) 1935

14 Junius P Erscheinungsformen und Ablauf der juvenilen Retinitis exsudativa macularis *Ztschr F Augenh 70* 129 1929

15 Davis W T & Sheppard E Juvenile macular exudative retinitis (Junius) *Arch Ophthal 13* 960–970 (June) 1935

16 Verhoeff F H & Grossman H P *Pathogenesis of disciform degeneration of the macula Arch Ophthal 18* 561–585 (Oct) 1937

17 Terry T L Discussion of paper by Verhoeff F G & Grossman H P (16) *Arch Ophthal 19* 46[illegible]–469 (March) 1938

18 Salvin S B & Furcolow M L Precipitins in human histoplasmosis *J Lab Clin Med 43* [illegible]59–2[illegible]4 (Feb) 1954

19 Maumenee A E Serous and hemorrhagic disciform detachment of the macula *Trans Pacif Cost Otoophthal Soc 40* 139–160 (May) 1959

20 Maumenee A E Symposium Macular diseases clinical manifestations *Trans Amer Acad Ophthal Otolaryng 69* 605–613 (July–Aug) 1965

21 Maumenee A E Symposium Macular diseases pathogenesis *Trans Amer Acad Ophthal Otolaryng 69* 691–699 (July–Aug) 1965

22 Mann W H Chorioretinitis due to histoplasmosis in clinical practice *Amer J Ophthal 55* 999–1006 (May) 1963

23 McCulloch C Histoplasmosis *Trans Canad Ophthal Soc 26* 107–197 (June) 1963

24 Jarvis G J & McCulloch C Ocular histoplasmosis *Canad Med Ass J 89* 1270–1273 (Dec) 1963

25 Walma D & Schlaegel T F Presumed histoplasmin choroiditis a clinical analysis of 43 cases *Amer J Ophthal 57* 107–110 (Jan) 1964

26 Van Metre T F & Maumenee A E Specific ocular uveal lesions in patients with evidence of histoplasmosis *Arch Ophthal 71* 314–324 (March) 1964

27 Van Metre T E Knox D L & Maumenee A E Specific ocular uveal lesions in patients with evidence of histoplasmosis and toxoplasmosis *South Med J 58* 479–486 (April) 1965

28 Schlaegel T F & Kenney D Changes around the optic nervehead In presumed ocular histoplasmosis *Amer J Ophthal 62* 454–458 (Sept) 1966

29 Schlaegel T F Weber J C Helveston E & Kenney D Presumed histoplasmic choroiditis *Amer J Ophthal 63* 919–925 (May) 1967

30 Krill A E Chishti M I Klein B A Newell F W & Potts A M Multifocal inner choroiditis *Trans Amer Acad Ophthal Otolaryng 73* 222–242 (March–April) 1969

31 Gass J D M Pathogenesis of disciform detachment of the neuroepithelium V Disciform macular degeneration secondary to focal choroiditis *Amer J Ophthal 63* 661–687 (March) 1967

32 Hyvarinen L Lerer R J & Knox D L Fluorescein angiographic findings in presumed histoplasmosis *Amer J Ophthal 71* 449–459 (Feb) 1971

33 Gass J D M & Wilkinson C I Follow up study of presumed ocular histoplasmosis *Trans Amer Acad Ophthal and Otolaryn* (in press)

34 Schlaegel T F Discussion of paper by Gass J D M & Wilkinson C P (33) (in press)

35 Falls H F & Giles C L The use of amphotericin B in selected cases of chorioretinitis *Amer J Ophthal 49* 1288–1298 (June) 1960

36 Giles C L & Falls H F Further evaluation of amphotericin B therapy in presumptive histoplasmosis chorioretinitis *Amer J Ophthal 51* 588–598 (April) 1961

37 Giles C L & Falls H F Amphotericin B therapy in the treatment of presumed histoplasma chorioretinitis A further appraisal *Amer J Ophthal 66* 101–104 (July) 1967

38 Leopold I H Drug therapy in uveitis Ocular Pharmacology and Therapeutics and the Problems of Medical Management Edited by J Kimura & E K Goodner Philadelphia F A Davis 1963 pp 1–32

39 Aronstam R H Histoplasmosis and the eye *Guthrie Clin Bull 36* 92–99 (Jan) 1967

40 Makley T A Long J W Suie T & Stephan J D Presumed histoplasmic chorioretinitis with special emphasis on the present modes of therapy *Trans Amer Acad Ophthal Otolaryn 69* 443–457 (May–June) 1965
41 Schlaegel T F Cofield D D Clark G & Weber J C Photocoagulation and other therapy for histoplasmic choroiditis *Trans Amer Acad Ophthal and Otolaryn 72* 355–363 (May–June) 1968
42 Newell F W & Krill A E Treatment of uveitis with azathioprine (Imuran) *Trans Ophthal Soc U K 87* 499–511 1967
43 Watzke R C & Snyder W B Light coagulation for hemorrhagic disciform degeneration of the macula *Trans Amer Acad Ophthal Otolaryn 72* 389–395 (May June) 1968
44 Krill A E & Archer D Choroidal neovascularization in multifocal (presumed histoplasmin) choroiditis *Arch Ophthal 84* 595–604 (Nov) 1970
45 Little H L Zweng H C & Peabody R R Argon laser slit lamp retinal photo coagulation *Trans Amer Acad Ophthal Otolaryng 74* 85–9 (Jan–Feb) 1970
46 Patz A Maumenee A E & Ryan S J Argon laser photocoagulation Advantages and limitations *Trans Amer Acad Ophthal Otolaryng 75* 569–579 (May–June) 1971
47 Gass J D M Photocoagulation of macular lesions *Trans Amer Acad Ophthal Otolaryng 75* 580–608 (May–June) 1971
48 L Esperance F A Argon and ruby laser photocoagulation of disciform macular disease *Trans Amer Acad Ophthal Otolaryng 75* 609–625 (May–June) 1971
49 Watzke R C & Leaverton P E Light coagulation in presumed histoplasmic choroiditis *Arch Ophthal 86* 127–132 (Aug) 1971
50 Coles R S *Steroid therapy in uveitis* International Ophthalmology Clinics Corticosteroids and the Eye. Boston Little Brown and Company 1966 Vol 6 pp 869–901
51 Smith J L & Jones D B Experimental avian ocular histoplasmosis *Arch Ophthal 67* 349–356 1962
52 Sethi K K & Schwarz J Experimental ocular histoplasmosis in pigeons *Amer J Ophthal 61* 538–543 (March) 1966
53 Schwarz J, Sethi K K & George E L Experimental histoplasmic iridocyclitis in chickens *Arch Path 83* 461–465 (May) 1967
54 Okudaira M & Schwarz J Experimental ocular histoplasmosis in rats A histopathologic study of immunogenic and hypersensitive ophthalmitis produced in rats by *Histoplasma capsulatum* and histoplasmin *Amer J Ophthal 54* 427 444 1962
55 Smith J L & Singer J A Experimental ocular histoplasmosis I The natural course of primary infection in the rabbit eye *Arch Ophthal 54* 3–6 (July) 1964
56 Smith J L Smith J A Goldwyn R H Hulvin S M & Pinnas G Experimental ocular histoplasmosis II Primary infection in the primate eye *Arch Ophthal 58* 226–230 (Aug) 1964
57 Smith J L & Singer J A Experimental ocular histoplasmosis III Experimentally produced retinal and choroidal lesions *Arch Ophthal 58* 413–423 1964
58 Smith J L & Singer J A Experimental ocular histoplasmosis IV Fluorescein fundus photographs of choroiditis in the primate *Arch Ophthal 10?1–10?6* (Dec) 1964

59 Schlaegel T F Swinton S Weber J C & Moorman R S A comparison of the intraocular reaction of rabbits to yeast phase and mycelial phase histoplasmin *Exp Eye Res 4* 162–167 1965
60 Sethi K K & Schwarz J Amphotericin B in ocular histoplasmosis of rabbits *Arch Ophthal 75* 818–825 (June) 1966
61 Salfelder K Schwarz J & Akbarian M Experimental ocular histoplasmosis in dogs *Amer J Ophthal 59* 290–299 (Feb) 1965
62 Salfelder K & Schwarz J *Histoplasma capsulatum* and chickens *Mykosen 10 8* 337–350 (March) 1967
63 Daniels L S Berliner M D & Campbell C C Varying virulence in rabbits infected with different filamentous strains of *Histoplasma capsulatum J Bact 96* 1535–1539 (Nov) 1968
64 Wong V W & Green W R *Experimental ocular histoplasmosis* Wilmer Residents Meeting April 1971
65 Asbury T The status of presumed ocular histoplasmosis Including a report of a survey *Trans Amer Ophthal Soc 64* 371–400 1966
66 Zeidberg L D The microdistribution of histoplasmin sensitivity in an endemic area Proceedings at the Conference on Histoplasmosis 1952 Edited by M J Willis *Public Health Service Publication 465 Public Health Monograph 39* 1956 pp 190–197
67 Knox, D L personal communication
68 Smith R L & Ganley J P An epidemiologic study of presumed ocular histoplasmosis *Trans Amer Acad Ophthal Otolaryn 75* 994–1005 (Sept-Oct) 1971
69 Furcolow M L High R H & Allen M F Some epidemiologic aspects of sensitivity to histoplasmin and tuberculin *Public Health Rep 61* 1132–1144 (Aug) (1946)
70 Smith R E & Ganley J P unpublished Walkersville data
71 Doto I L Furcolow M L Varga D T Tosh F E & Griffith R L Seasonal histoplasmin conversion rates in Lexington Ky *Arch Environ Health 15* 375–383 (Sept) 1967
72 Makley T A Long J & Suie T Uveitis in children A follow up study *J Ped Ophthal 6* 136–139 (Aug) 1969
73 Weber J C & Schlaegel T F Delayed skin test reactivity of uveitis patients Influence of age and diagnosis *Amer J Ophthal 67* 732–737 (May) 1967
74 Weber J C Schlaegel T F & Chapman J S Atypical mycobacteria and uveitis *Amer J Ophthal 72* 167–170 (July) 1971
75 Schlaegel T F & Weber J C Follow up study of presumed histoplasmin choroiditis *Amer J Ophthal 71* 1192–1195 (June) 1971
76 Maumenee A E Clinical entities in uveitis An approach to the study of intraocular inflammation *Amer J Ophthal 69* 1–27 (Jan) 1970
77 Suie T Rheins M S & Makley T A Serologic studies of presumed histoplasmic choroiditis *Amer J Ophthal 60* 1059–1061 (Dec) 1965
78 Kaufman L Terry R T Schubert J H & McLaughlin D Effects of a single histoplasmin skin test on the serologic diagnosis of histoplasmosis *J Bact 95* 798–803 (Oct) 1967
79 Schlaegel T F Histoplasmic choroiditis *G P 35* 98–103 (Feb) 1967
80 Schlaegel T F Presumed histoplasmic choroiditis *Int Ophthal Clin 7* 561–582 (Fall) 1967

81 Schlaegel T F *Essentials of uveitis* Boston, Little Brown and Company 1969 pp 155–163
82 Leinfelder J T Ocular histoplasmosis (a survey) *Survey of Ophthal 1?* 103–111 196
83 Smith R. E. & Ganley J P Presumed ocular histoplasmosis I Histoplasmin skin test sensitivity in cases identified during a community survey *Arch Ophthal* (in press)
84 Smith, R. E., Ganley J P & Knox, D L Presumed ocular histoplasmosis II Patterns of peripheral and peripapillary scarring in persons with non macular disease *Arch Ophthal* (in press)
85 Hoefnagels K. L. J & Pijpers P M. *Histoplasma capsulatum* in a human eye. *Amer J Ophthal 63* 715–23 (April) 196
86 Perkins E. S Uveitis survey at the Institute of Ophthalmology London. Clinical Methods in Uveitis Edited by S B Aronson, C N Gamble E. K. Goodner & G R O Connor Saint Louis The C. V Mosby Company 1968 pp 58–65
87 Ellis F D & Schlaegel T F Geographic distribution of presumed histoplasmic choroiditis *Invest Ophthal 10* 468 (June) 1971 (abstract)
88 High R. H., Zwerling H. B & Furcolow M. L Disseminated pulmonary calcification. *Public Health Rep 6.* ?0–29 (Jan.) 194?
89 *Maumenee A E* In discussion of paper by Krill A E., et al (30)
90 Edwards L. B Aquaviva, F A., Livesay V T., Cross F W & Palmer C. E. An atlas of sensitivity of tuberculin PPD B and histoplasmin in the United States *Amer Rev Resp Dis 99* (Part 2) 1–132 (April) 1969
91 Furcolow M L., Balows, A., Menges R. W., Pickar D., McClellan, J T & Saliba, A Blastomycosis An important medical problem in the central United States *JAMA 198* 529–532 (Oct.) 1966
92 Campbell, C. C. Use and interpretation of serologic and skin tests in the respiratory mycoses Current considerations *Dis Chest 54* (supplement No 1) 49–54 (Oct) 1968
93 Systemic mycosis Hard to diagnose – dreadful to treat. *Medical World News* July 3 1970 pp 34–40
94 Spaeth, G L. Absence of so-called histoplasma uveitis in 134 cases of proven histoplasmosis *Arch Ophthal* ? 41–44 (Jan.) 196?
95 Comstock, G W., Vicens C. N Goodman, N L. & Collins S Differences in the distribution of sensitivity to histoplasmin and isolations of *Histoplasma capsulatum Amer J Epidem 88* 195–209 196?
96 Guld J Quantitative aspects of the intradermal tuberculin test in humans II The relative importance of accurate injection technique *Acta Tuberc Scand 30* 16–36 1954
97 Ganley J P., Smith R. E Thomas D B Comstock G W & Sartwell P E Booster effect of histoplasmin skin testing in an elderly population *Amer J Epid 95* 104–110 (Feb) 19?
98 Grzybowski S & Allen E A The challenge of tuberculosis in decline A study based on the epidemiology of tuberculosis in Ontario Canada *Amer Rev Resp Dis 90* ?0 – ? (Nov) 1964
99 Krause A K Studies in immunity to tuberculosis Experimental studies on the cutaneous reaction to tuberculo protein *J Med Res 35* 1–23 (Sept) 1916
100 Cochran, W G Some methods for strengthening the common χ tests *Biometrics 10* 417–4? (Dec) 1954

101 Bronson S M & Schwarz J Roentgenographic patterns in histoplasmosis *Amer Rev Tuberc Pul Dis 76* 173–194 (Aug) 1957
102 High R H & Zwerling H B Variation with age in the frequency of tuberculous pulmonary calcification *Public Health Rep 61* 1769–1782 (Dec) 1946
103 Salfelder K & Schwarz J *Histoplasma capsulatum* and chickens *Mykosen 10 8* 337–350 (March) 1967
104 Bauman D S & Chick E W An experimental model for studying extrapulmonary dissemination of *Histoplasma capsulatum* in hamsters *Amer Rev Resp Dis 100* 79–81 1969
105 Potts A M An hypothesis on macular disease *Trans Amer Acad Ophthal Otolaryng 70* 1058–1062 (Nov–Dec) 1966
106 Chaparas S D Sheagren J N MeMeo A & Hedrick S Correlation of human skin reactivity with lymphocyte transformation induced by mycobacterial antigens and histoplasmin *Amer Rev Resp Dis 101* 67–73 1970
107 Kirby G R Correlation of tuberculin skin reaction with *in vitro* lymphocyte transformation *Amer Rev Resp Dis 97* 904–908 1968
108 McFarland W & Heilman D H Comparison of lymphocytic transformation and intradermal reactions to tuberculins *Amer Rev Resp Dis 93* 742–748 1966
109 Adamson D M & Cozad G C Effect of antilymphocyte serum on animals experimentally infected with *Histoplasma capsulatum* or *Cryptococcus neoformans J Bact 100* 1271–1276 (Dec) 1969
110 Goodwin R A & Snell J D The enlarging histoplasmoma *Amer Rev Resp Dis 100* 1–12 1969
111 Vanek J & Schwarz J The gamut of histoplasmosis *Amer J Med 50* 89–104 (Jan) 1971
112 Hasenclever H F Shacklette M H Young R V & Gelderman G A The natural occurrence of *Histoplasma capsulatum* in a cave 1 Epidemiologic aspects *Amer J Epidem 86* 238–245 1967
113 Salvin S B Immunization of mice against *Histoplasma capsulatum* Proceedings at the Conference on Histoplasmosis 1952 Edited by M J Willis *Public Health Service Publication 465 Public Health Monograph 39* 1956 pp 107–109
114 Bauman, D S & Chick E W Immunoprotection against extrapulmonary histoplasmosis in hamsters *Amer Rev Resp Dis 100* 82–85 1969
115 Johnson W W Smith D T & Vandiviere M H New aspects of mycobacterial skin tests III Simultaneous or sequential infection with different mycobacteria *Arch Environ Health 11* 37–49 (July) 1965
116 Walter J E The significance of antibodies in chronic histoplasmosis by immunoelectrophoretic and complement fixation tests *Amer Rev Resp Dis 99* 50–58 1969
117 Heusinkveld R S Tosh F E Newberry W M Ciccone P J & Chin T D Y Antibody response to the histoplasmin skin test *Amer Rev Resp Dis 96* 1069–1071 (Nov) 1967
118 Waldorf D S Wilkens R F & Decker J L Impaired delayed hypersensitivity in an aging population *JAMA 203* 831–834 (March) 1968
119 Kuemmerer J M & Comstock G W Sociologic concomitants of tuberculin sensitivity *Amer Rev Resp Dis 96* 885–897 (Nov) 1967
120 Palmer K N V The role of smoking in bronchitis *Brit Med J 1* 1473–1474

191 Bettman J W Fellows V & Chao P The effect [illegible] on the intraocular circulation *Arch Ophthal* 59 451-4 [illegible]
192 Friedman E Choroidal blood flow *Arch Ophth* [illegible]
193 Gamble C N Aronson S B & Brescia F B [illegible] I The production of recurrent immunologic (Aver) [illegible] relationship to increased uveal vascular permeability *Arch O* [illegible]
194 Aronson S B Fish M B Pollycove M & C [illegible] vascular permeability in ocular inflammatory disease *A* [illegible] (April) 1971

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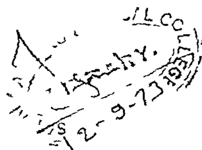
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OFFICIAL TRANSACTIONS

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Sunday June 20th

Official Opening of the Congress at the University of Iceland Reykjavik

Monday June 21st

Thomassen T L The Intraocular Pressure An introduction 7
Svedberg B & Bill A Scanning electromicroscopy in the studies of the canal of Schlemm trabecular meshwork and corneal endothelium in human eyes 11
Tonjum A A new sensor for pneumatic tonometry Construction and working principle 12
Kessing S V Trabeculotomy ab externo 20
Goldschmidt E The heredity of glaucoma 27
Vannas A Vascular changes in pseudoexfoliation of the lens capsule and capsular glaucoma 32
Aasved H Trabeculotomy trabeculectomy and sinustomy – some clinical results 33
Vannas Salme & Linkova M Adrenalin therapy in glaucoma 39
Bertelsen T I & Syversen K Experience with keratoprosteses 45

Grop K H V Clinical and histological findings in crystal line corneal dystrophy 52
Horven I Nornes H Syrdalen P & Tønjum A Dynamic tonometry in carotid occlusive disease 58

Wednesday June 23rd

Ehlers H Ophthalmological involvements in diabetes An introduction 59
Walinder P-E Wadman B Andersson L & Svedbergh B Pregnancy and diabetic retinopathy 66
Hvidberg Hansen J Pigment granules in iris pigment epithelium of diabetics 68
Tønjum A & Green K Influence of some agents on corneal permeability of fluorescein *in vitro* 76
Odland M & Aasved H Follow up of initially nonglaucomatous patients with fibrillopathia epitheliocapsularis so called senile exfoliation of the anterior lens capsule 77
Ehlers N Importance of callosal transfer in the extramacular inhibition phenomenon along the hemiopic border 82
Rosengren B Significance of subretinal absorption for effectiveness of buckling operations 87
Madsen P H Experiences in surgical treatment of the haemorrhagic glaucoma A follow up study 88

GENERAL MEETING

Report on N O L R 92
Report on Acta Ophthalmologica 92
Presentation of the K K K Lundsgaard Medal 92
Members of Congress 94

ACTA OPHTHALMOLOGICA
XX MEETING OF NORDIC OPHTHALMOLOGISTS
Reykjavik Iceland 20-24 June 1971

THE INTRAOCULAR PRESSURE

An Introduction

BY

THORE LIE THOMASSEN

More than any other field within ophthalmology the pressure in the eye has been a subject of research writing and discussion through the past 120 years This is no doubt partly because it is a matter of immense importance in our practical clinical work but also because it has a fascination of its own

The student probably has a feeling of being face to face with a fairly substantial quantity about which it ought to be possible to acquire more knowledge but the pressure has always had a special ability to keep its secrets Time and again so many factors have proved to be operative that it is difficult to know what we are doing when applying a diagnostic method to the eye

True our knowledge has widely increased in the course of time but nevertheless it still has large and important gaps

The problems concerning the pressure in the eye may be divided in a simple manner into four groups

1 Measurement and measuring methods
2 Relation of the pressure to disease of the eye
3 The genesis pathogenesis and hereditary aspects of the pressure
4 Treatment.

Let us have a look at the first group Measurement and measuring methods

Sufficiently refined and reliable measuring methods are a presupposition for making progress Thanks to people like Schiötz Friedenwald and Goldmann we have methods applicable for ordinary clinical use but for research pur poses we could do with more refined methods

In particular the clinical methods are ill suited in cases where frequent let alone continuous measurements are desired The explanation is probably that each measurement affects the eye to such an extent that the results of continuous measurements become incalculable

One of the studies to be submitted here to day concerns a new measuring method Let us hope that it will get us closer to our aim

It is now almost 120 years since Albrecht von Graefe established that an elevated pressure in the eye was the cause of glaucoma What are our views now? I suppose we must say that von Graefe was right but the relation between pressure and disease is none the less fraught with unsolved problems

For a long time we have been aware of the existence of a disease very similar to glaucoma but in which the pressure is normal – so called pseudoglaucoma We must admit that as yet we do not understand this disease although recently it has been claimed but not substantiated that in these cases the eye is unable to tolerate the normal pressure and that the disease can be stopped if only the pressure is kept low enough

In recent years a new difficulty has cropped up – the question whether there is a type of ocular hypertension which does not cause glaucoma At least this is indicated by mass surveys There is more probably a question mainly of pressure which is only slightly above what is considered the border line value This may give especially the practitioners food for thought *A priori* the diagnosis of incipient glaucoma may be very difficult and unreliable and now perhaps we have to be even more sceptical We look back upon the numerous patients who have been treated successfully through decades without any loss of function having occurred Have these patients in fact had glaucoma?

A problem which was much discussed in the twenties and thirties especially in connection with optic atrophy in tabes dorsalis was a possible significance of the relationship between the blood pressure and the intraocular pressure This problem is now again topical because of the extensive use of antihypertensive agents We gain the impression that occasionally there is a striking progression of glaucoma in connection with such medication To my knowledge there has not yet been any systematic investigation in this field but it is certainly a factor which merits attention

This leads us to a more general question What mechanism makes increased intraocular pressure harm the eye? The classic explanation that the lamina cribrosa is so weak that it is pressed backward can hardly be the whole truth

We know there must be something special about the blood circulation in the eye as the venous pressure must always be at least a bit higher than the intraocular pressure as long as the circulation is maintained When the intra ocular pressure rises in glaucoma the venous pressure must rise as well and the intraocular pressure and thereby also the venous pressure may exceed the diastolic arterial pressure

Obviously a high venous pressure must be associated with very special conditions in the small vessels conditions which must be assumed to involve poor nutrition in the areas supplied by them To day we know in theory that no doubt these are probably very important factors but we must admit that we are utterly ignorant of the mechanism This is something which positively cries out for investigation

The third problem is the genesis pathogenesis and heredity of the pressure As early as the past century Leber maintained that the aqueous humour was a secretion and that it flowed out of the eye through Schlemm s canal This was not generally accepted and it was persistently claimed that the aqueous humour was a tissue fluid which like other tissue fluids was formed in the arterial part and returned to the blood in the venous part of the capillaries The final proof was not adduced until about 30 years ago It was Davson s demonstration that the aqueous was osmotically hypertonic in relation to the blood which substantiated that it must be a secretion and it was Ascher s finding of the aqueous veins which revealed a continuous flow of aqueous humour from the eye through the trabecular meshwork and Schlemm s canal Since this was realized we have been living in what I should like to call the hydrodynamic epoch It has brought much useful information Strange though it may seem it was not until these years that the entire mechanism of narrow angle glaucoma was generally accepted although it had been dis cussed in the literature for more than a hundred years

The other important realization is that the greatest resistance to the outflow is in the trabecular meshwork and that it is increased resistance in this site which usually is responsible for the elevated pressure The trabecular meshwork is on the whole the central factor in to day s pressure problems Anything which can increase our knowledge of its structure and function is of great value The fine structure of the trabecular meshwork will be described in one of the papers to be presented

Coming from Norway I cannot help devoting a few words to the so called exfoliation syndrome Interest in this syndrome has been particularly intense in Finland and Norway Recent research has elucidated that this is a disease *sui generis* and that the capsular glaucoma must be interpreted as a secondary phenomenon presumably more malignant than an ordinary glaucoma simplex

Two of the papers that we shall hear here are expected to elucidate new aspects of the exfoliation syndrome

There is however an important field which I suppose we have not forgotten but which has not been much to the fore in the past few decades I am re ferring to the central nervous regulation of the pressure We know that it must exist Suffice it to point out the diurnal fluctations in the pressure which follow so many other fluctuations in organic functions all of which are be lieved to have their centre in the basal ganglia This is an aspect of which we know next to nothing It was interesting to see in a recent publication in Acta ophthalmologica the suggestion that perhaps the water drinking test did not act direct upon the eye but via an osmotic action upon the nervous pressure regulating centre It is not altogether unlikely that at some future time it will be discovered that the primary cause of open angle glaucoma is a defect in the central pressure regulation In am thinking particularly of the periodical increases in the pressure in incipient glaucoma which makes an impression of being functional disorders

The fourth main subject is *treatment* Not less than three of the papers to be submitted to day deal with the treatment I shall not enlarge on this subject but merely state that as we believe the cause of open angle glaucoma to be increased resistance in the trabecular meshwork it seems logical to attack the trabecular meshwork in attempts at improving the outflow of the aqueous humour

In conclusion it is my wish that the papers and discussions to follow may take us a bit onward and afford inspiration for further research

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*From the Department of Pharmacology (Head Professor E H Barany)
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SCANNING ELECTRON MICROSCOPIC STUDIES OF THE CORNEAL ENDOTHELIUM IN MAN AND MONKEYS

BY

BJÖRN SVEDBERGH and ANDERS BILL

Published in Acta Ophthalmologica Vol 50 321 1972

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(Head Professor Thore Lu Thomassen)*

A NEW SENSOR FOR PNEUMATIC TONOMETRY

Construction and working principle

BY

ASBJORN M TONJUM

A pneumatic tonometer has been described Particular attention has been paid to the construction and working principle of the sensor which enables a continuous recording of the intraocular pressure and its varia tions in both human eyes and eyes of even conscious animals

Key words pneumatic tonometer – tonometry – sensor – continuous – intraocular tension

Introduction

A pneumatic tonometer was described by Durham Bigliano and Masino in 1965 An improved model was reported on by Langham and McCarthy (1968) In brief the working principle was that a thin membrane supported by gas pressure applanated the cornea or sclera The gas pressure at which a pre determined area was applanated was recorded These tonometers allowed only a momentary recording of the intraocular pressure thus comparable to that obtained with Mackay Marg s tonometer (1959)

The purpose of this paper is to give a brief presentation of a new sensor for pneumatic tonometry allowing the intraocular pressure to be recorded continuously In addition the measurements are easier to perform and are more reproducible than with the previous pneumatic tonometers

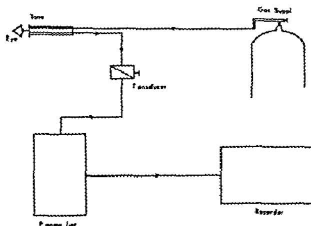


Fig 1
The pneumatic tonometer system with the connections between the different parts

The Tonometer

A commercial model of the tonometer is available* It has a built in gas container only one chart speed and the recorder has one sensitivity the scale reading gives the intraocular pressure directly in mmHg

For many purposes however it is important to be able to select a convenient *sensitivity of the recording equipment and a suitable speed of the chart* Therefore it will now be dealt with a more versatile assembly of the different parts of which the tonometer system consists The sensor an oxygen gas container a pressure electric transducer and a recording unit consisting of a preamplifier and a two channel recorder with a zero suppression (Fig 1) Particular attention will be paid to the sensor which is shown in Fig 2 and schematically in Fig 3

The gas is led from the container through a pore system within the sensor thus providing an airbearing for the piston which moves frictionless or floating in axial direction Some of the gas escapes into the air from the thin layer surrounding the piston and partly it passes back into the gas chamber within the sensor Through the whole length of the piston is a hole leading to the tip of the sensor ending behind the silicone rubber membrane From this space the gas leaves into the air through six small holes in the endplate of the sensor

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The Applamatic Tonometer is manufactured by Block Engeneering Inc Cambridge, Massachusetts USA

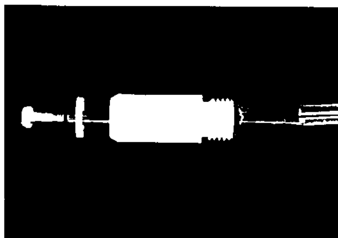


Fig 2
The sensor The handle is removed

tip The endplate has a diameter of 4 mm and the holes in it are arranged in a circle around the central opening The membrane is easily replaceable and may be cleaned with 70 % isopropylalcohol It is 5 mm in diameter and has a central area of 5 μ in thickness

During a measurement of the intraocular pressure the sensor is moved on to the eye with the silicone rubber membrane placed tangentially on the cornea after topical anesthesia The membrane will then be pressed towards the endplate of the sensor tip thus preventing the flow of gas through the central

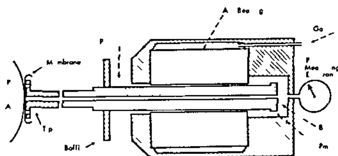


Fig 3
Cross section of the sensor schematically A applanated area B piston C cornea P_e intraocular pressure M gas chamber within the sensor connected with the pressure transducer P_m gas pressure within the gas chamber

opening and also the escape of gas to the air This results in an increasing pressure within the gas chamber which in turn pushes the membrane more strongly against the cornea which will be applanated When a certain area (A) of the cornea is applanated there is an equilibrium between the intraocular pressure (P_e) and the gas pressure behind the membrane and in the gas chamber The size of this area is by the manufacturer assumed to be 16 6 mm or having a diameter of 4 56 mm Because of the geometry of the sensor tip this area will automatically be applanated and in this state the membrane acts as a valve which opens and closes at a high rate which may be heard as a high pitched tone The pressure in the gas chamber (P_m) will be transmitted through a tubing to the pressure electric transducer and from here the electric impulses are fed into the preamplifier and the recorder

The forces which applanates the cornea (A p) has to be equal to the forces pushing the piston forward B p_m where B is the net area of the piston on which *the measured pressure acts Thus* p_e A = p_m B *However during* a measurement the pressure behind the membrane varies from region to region *within this space partly because it is a dynamic rather than a static equilibrium* The average pressure equals the intraocular pressure (p) But the pressure which is registered (p_m) is higher than the average one *In the* present sensor there is a fixed relationship between p_m and p pm = G_p p where the factor G_p is numerically about 2 1 Thus the applanated area is 2 1 times as wide as the piston area 2 1 7 9 mm = 16 6 mm with a diameter of 4 56 mm It is evident that the force needed to applanate this area increases with in creasing intraocular pressure But it is independent of the position of the piston along its axis Thus during a measurement it may stay anywhere within its range of free floating movement without any significant influence upon the scale reading This is of particular importance for the continuous recording of the intraocular pressure and its variations

Other factors which make it necessary to modify the basic theory are the membrane bending forces which are difficult to evaluate

An empirical calibration of the relationship between the intraocular pressure and the scale readings of the complete tonometer systems is therefore essential

Operation and Calibration

We have used a Sanborn differential pressure transducer (267b) a carrier preamplifier (350 1100AS) and a Sanborn two channel recorder For recording the intraocular pressure a sensitivity setting of 0 4 mV/mm was convenient

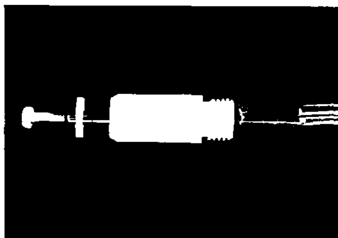


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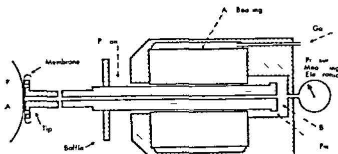


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Cross section of the sensor schematically A applanated area. B piston C cornea P_e intraocular pressure M gas chamber within the sensor connected with the pressure transducer P_m gas pressure within the gas chamber

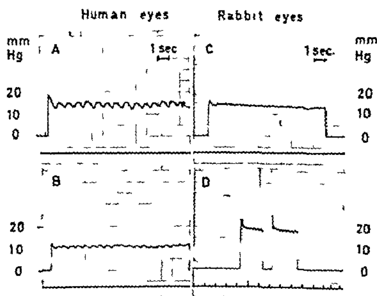


Fig 5
Recordings of the intraocular pressure of eyes from two persons (A and B) and of rabbit eyes from two different animals (C and D)



Fig 6
Recording of the intraocular pressure of a human eye To the left the recording equipment had a sensitivity setting of 0 4 mV/mm scale deflection To the right the sensitivity was increased ten times in order to study the pulse synchronous variations of the intraocular pressure

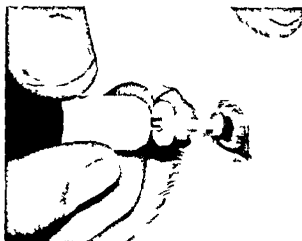


Fig 4
Measurement of the intraocular pressure of a conscious rabbit after topical anesthesia

The gas was supplied from an oxygen container at a pressure of 20 lbs /sq in or 1 6 kg/cm This pressure will be greatly reduced particularly while flowing through the pore system for the airbearing within the sensor

The sensor may be held in any position but preferably in such a way the tip points horizontal or downwards During a measurement the membrane of the sensor is placed tangentially on the cornea after topical anesthesia The patient may be seated or laid down Each measurement may last for 10–15 seconds but may as well be extended for several minutes Fig 4 shows a measurement of a conscious rabbit and Fig 5 shows the recording of the intraocular pressure of 2 human eyes as compared with 2 rabbit eyes

Fig 6 shows an example of how it is possible to study the ocular pulse wave and pulse pressure in more detail when the sensitivity of the recording equipment is increased ten times

It is not the purpose to give an extensive report on the calibration problems An example of pneumatic tonometry along with open and closed manometry of 3 dead rabbit eyes *in situ* is shown in Fig 7 The anterior chamber had been cannulated and by means of the saline reservoir the intraocular pres sure was set between 5 and 50 mmHg with stepwise intervals of 5 mmHg (abscissa) The ordinate represents the scale readings at the standard sensitivity of the system It appears to an approximately linear relationship between the intraocular pressure and the average of the scale readings in these 3 rabbit eyes However there is a difference between the readings with open and closed

stopcock manometry and this difference increases with increasing intraocular pressure This indicates that there is some increase of the intraocular pressure during a measurement

Fig 8 demonstrates a manometric recording with cannulation of the anterior chamber of a rabbit eye under closed stopcock conditions The animal had been given Nembutal (Abbott) intravenously Simultaneously the intraocular pressure was recorded with the pneumatic tonometer During this measurement there was an increase of 7–8 mmHg at this pressure level (P_0) of about 33 mmHg

A similar response has been found also in human eyes The increase of the intraocular pressure during the measurement is larger than with Goldmann s applanation tonometer but considerably less than with Schiotz tonometer

Acknowledgment

I am indepted to Robert Webb *Ph D* of the *Block Engeneering Inc* Cambridge Massachusetts USA for providing the sensor of the pneumatic tonometer and valuable informations This work has been supported by US Public Health Service Grant EY 00476-05

References

Durham D G Bigliano R P and Masino J A (1965) Pneumatic applanation tonometer *Trans Amer Acad Ophthal Otolaryng* 6 1099–1041

Langham M E and McCarthy Elisabeth (1968) A rapid pneumatic applanation tonometer Comparative findings and evaluation *Arch Ophthal* 79 389–399

Mackay R S and Marg E (1959) Fast automatic electronic tonometers based on an exact theory *Acta ophthal (Kbh)* 3[illegible] 495–50[illegible]

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From the University Eye Clinic
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Rigshospitalet Copenhagen

TRABECULOTOMY AB EXTERNO

BY

SVEND VEDEL KESSING

During recent years microsurgery has opened up new possibilities for the surgical treatment of glaucoma by operative procedures applied direct to Schlemm s canal
The present report deals with the experience of trabeculotomy *ab externo* on 26 eyes affected with various forms of glaucoma
This procedure appears to be less traumatizing than the conventional filtering operations and the preliminary results based upon postoperative follow up periods of 1-6 months are extremely promissing

Key words glaucoma – surgery – trabeculotomy *ab externo*

Introduction Method and Material

During the past decade ophthalmological microsurgery has been gaining increasing ground The use of a microscope in operations on the eye affords not only a possibility of a technically perfect operation but also permits procedures which have not previously been practicable

This applies in particular within the treatment of glaucoma where the common complications to the conventional filtering glaucoma operations have encouraged to trying entirely new procedures

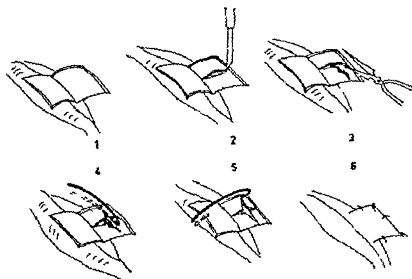


Fig 1
Technique of trabeculotomy *ab externo* (Dannheim & Harms 1969)

At present there is a choice of 3 different microsurgical methods for treating glaucoma Trabeculotomy *ab externo* (Dannheim & Harms 1969) trabeculectomy (Cairns 1968) and sinusotomy (Krasnov 1968) I am reporting the experience of trabeculotomy *ab externo* This method is still so new that a publication of the results seems justified although the material is small and the *follow up period short*

The technique is illustrated in Fig 1 (Dannheim & Harms 1969) After creating a conjunctival flap and a 2 × 3 mm corneo scleral flap both corneally based Schlemm s canal is located by a radial section into the scleral window at a magnification of 20–40 ×

After its outer wall has been cut at the site of the scleral window Schlemm s canal is entered by one limb diameter 1 mm of a 10 mm U shaped probe The probe is then rotated 90° so that the limb is visible in the anterior chamber Thus the trabecular meshwork is ruptured The same procedure is performed in the opposite direction in Schlemm s canal Lastly the scleral window is *firmly closed as a conjunctival filtering bleb is to be avoided*

In order to be able to locate the canal with certainty it has proved of essential importance to make the scleral flap as thick as possible, i e at least three quarters of the sclera s thickness In this procedure the scleral spur is usually distinctly visible at the bottom of the scleral window and Schlemm s

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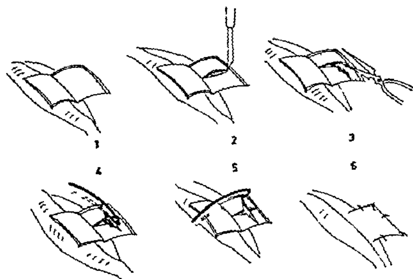


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Table I
Composition of the material and operative complications

	No eyes	Canal discovered	Not discovered	Corneal lesions	Iris prolapse
Congenital glaucoma					
infants older than 6 year	5	4	1	1	0
adults	1	1	0	0	0
Secondary glaucoma					
uveitis	2	2	0	0	1
aniridi	2	1	1	0	0
Sturge Weber	1	1	0	0	0
Open angle glaucoma	9	9	0	2	0
Chron narrow angle glaucoma + iridectomy	6	4	2	0	0
Total	26	22	4	3	1

canal is immediately corneal to this site A reliable sign that the instrument is in Schlemm s canal is incidentally the presence of the typical fibrillar trabecular pattern visible at a magnification of 40 ×

As a rule the chamber does not empty and immediately after the rupture of the trabecular meshwork there occurs a fine serrated bleeding into the chamber on the anterior surface of the iris in the area where the trabecular meshwork was broken This haemorrhage usually subsides in 24 hours The present report concerns 26 operations on various types of glaucoma except acute narrow angle glaucoma Table I gives the composition of the material

Complications

The operative complications are apparent from Table I

Schlemm s canal could not be located in 4 cases so that the procedure had to be changed to a filtering operation

It is surprising that Schlemm s canal could not be located in 2 out of 6 cases of chronic narrow angle glaucoma Possibly Schlemm s canal had col

Table II

Postoperative complications in cases where Schlemm's canal could be located

	No eyes	Filtering bleb	Delayed resorbtion of haemorrhage	Cyclodialysis
Congenital glaucoma				
infants older than 6 year	4	1	0	0
adults	1	0	0	0
Secondary glaucoma				
uveitis	2	0	0	0
aniridi	1	0	0	0
Sturge Weber	1	1	0	0
Open angle glaucoma	9	1	2	1
Chron narrow angle glaucoma + iridectomy	4	0	0	0
Total	22	3	2	1

lapsed in these two cases The corneal injuries occurred during the rotation of the probe in the chamber Descement's membrane being damaged peripherally in the cornea These injuries have proved negligible

In one case prolapse of the iris occurred due to an injury to the trabecular meshwork in the scleral window

The postoperative complications in the 22 cases where trabeculotomy could be carried through are listed in Table II

The 3 cases of a filtering bleb are presumably due to insufficient suturing of the scleral flap

In 2 instances there was bleeding into the chamber which did not subside in 24 hours as is usual In both cases the bleeding subsided spontaneously in 8–10 days without sequelae

In one case postoperative gonioscopy revealed a backward directed cleft to the ciliary body as seen in cyclodialysis

The operation did not in any case entail cataract or progression of pre existing cataract

Table III

Results in cases where Schlemm's canal could be located

Time Pressure (mm Hg)	1 m ≤ 20	 >20	2 m ≤ 20	 >20	4 m ≤ 20	 >20	5 m ≤ 20	 >20	6 m ≤ 20	 >20	Total No	Pressure contr No
Congenital glaucoma												
infants older than 6 year	–	–	1	–	–	–	–	–	2	1	4	3
adults	–	–	–	–	–	–	–	–	1(+)	–	1	1
Secondary glaucoma												
uveitis	2	–	–	–	–	–	–	–	–	–	2	2
aniridi	–	–	–	–	1	–	–	–	–	–	1	1
Sturge Weber	–	–	–	–	–	–	–	–	1	–	1	1
Open angle glaucoma	3	–	2	–	2	–	1	–	1	–	9	9
Chron narrow angle glaucoma + iridectomy	1	–	3	–	–	–	–	–	–	–	4	4
Total											22	21

Results

The preliminary results are apparent from Table III The minimum post operative follow up period was 1 month A pressure of ≤ 20 mm was demanded to consider the case controlled It was only in one case that supplementary medication was required to keep the pressure ≤ 20 mm

On the basis of these criteria 21 out of the 22 cases in which Schlemm s canal was located were in control

In 15 out of the 22 cases postoperative gonioscopic inspection could be performed At follow up one month after the operation compression by the gonioscope caused bleeding into the chamber by way of the aqueous veins through the ruptured trabecular meshwork in 10 cases (cf Table IV)

In 9 cases we have done pre and postoperative tonography on the same eyes The average preoperative C value was 0 09 and the postoperative value 0 20

Table IV
Postoperative gonioscopic examination

	15 eyes ≤ 20 mm
No visible rupture in the meshwork	2*
Gaping of the meshwork	3
Gap + entrance of blood by impr – goniosc ex	10

* One eye with cyclodialysis and one with med therapy

Discussion

From the present material it is apparent that trabeculotomy *ab externo* by the technique used is practicable and that despite the limited experience of the method the operation does not cause serious complications This in particular renders the method advantageous as compared with the filtering glaucoma operations and ought to make for more liberal indications

Moreover the operation may be repeated several times on the same eye Lastly unlike goniotomy in buphthalmic eyes this procedure may be carried out even though the cornea is cloudy In buphthlamic eyes it also affords an

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Moreover the operation may be repeated several times on the same eye Lastly unlike goniotomy in buphthalmic eyes this procedure may be carried out even though the cornea is cloudy In buphthlamic eyes it also affords an

important information viz whether Schlemm s canal is present or whether it has undergone atrophy In the latter event repeated goniotomies will be of no avail and a filtering operation has to be chosen

As for results of the operation the follow up period in the present material is of course too short for any final conclusions However the preliminary results are extremely satisfactory especially in the groups buphthalmos and glaucoma simplex

It should be mentioned however that repeated postoperative impression gonioscopic studies have shown decreasing haemorrhage into the anterior chamber indicating increasing cicatricial changes in the trabeculotomy scar It has to be expected therefore that some of the patients will develop elevated pressure so that supplementary medication will be required

Finally it may be pointed out that the procedure affords a possibility of new pathophysiological observations As already mentioned it proved im possible to locate Schlemm s canal in a few cases of the present small material primarily cases of chronic narrow angle glaucoma Accordingly the increased outflow resistance in eyes with chronic narrow angle glaucoma may also be due to collapse of Schlemm s canal A few authors have previously suggested similar ideas (Nesterov 1970)

References

Cairns J E (1968) Trabeculectomy *Amer J Ophthal 66* 673–6 9

Dannheim R & Harms H (1969) Technik, Erfolge und Wirkungsweise der Trabe kulotomie *Klin Mbl Augenheilk 155* 630–63

Krasnov M M (1968) Externalization of Schlemm s canal (Sinusotomy) in glaucoma *Brit J Ophthal 52* 157–161

Nesterov A P (1970) Role of the blockade of Schlemm s canal in pathogenesis of primary open angle glaucoma *Amer J Ophthal 70* 691–696

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From the Department of Ophthalmology
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THE HEREDITY OF GLAUCOMA

BY

E GOLDSCHMIDT

In ophthalmological text books e g Duke Elder 1969 it is stated that primary glaucoma simplex is of genetic nature However it has never been proved that the glaucoma of old age is particularly dependent upon inherited factors This will be further elucidated below with particular emphasis upon the type of most quantitative importance viz open angle glaucoma in elderly persons

I am by no means contesting that glaucoma often runs in families and that the types occurring at an early age are predominantly or exclusively genetically determined

Congenital glaucoma is often observed in siblings with a high frequency of consanguinity in the parents and thus shows conformity with recessive trans mission On the other hand serial investigations have shown that sporadic cases of congenital glaucoma are considerably more common than familial cases Where Denmark is concerned this has been substantiated by Westerlund in 1947 and confirmed by many others At the University Eye Clinic in Odense we have had in the course of the past 5 years 17 patients with primary con genital glaucoma all sporadic cases

Infantile or juvenile glaucoma is often transmitted by a dominant mode of inheritance In Scandinavia Jerndal in 1970 published a family in which the disease could be traced through 8 generations In this case there was no doubt about the genetic aetiology of the disease

In the more advanced age groups the frequency of glaucoma increases rapidly

Thus reports on several cases in a sibship or in two successive generations do not by any means afford a proof of the significance of hereditary factors in the development of glaucoma

There have been only a few major proband studies In these cases the pro positi have been selected in eye clinics and it is doubtful whether they can be said to be representative of the glaucoma population Although this is assumed the serial investigations have shown that only a minor proportion of the pro positi have a history of glaucoma in the immediate family i e in siblings or parents Far more than half the propositi represent sporadic cases

To decide whether a property or a disease is of genetic nature twin studies are of particular value In the case of glaucoma in old age there have been no major twin studies but in a few case reports both concordance and dis cordance have been found

Through the Danish Register of Twins we have tried to trace Danish twins with glaucoma We succeeded in finding a total of 7 pairs in which one twin had confirmed open angle glaucoma Only in one case did the other twin also have glaucoma Therefore this material cannot afford information of any value concerning the significance of genetic factors

Twin studies are presumably the only practicable way of procuring further information but let me point out that the collection of a suitable large material is an almost insurmountable task and possible only in places where current registration and life long follow up of twins is already being practised

Only by demonstrating a higher concordance in monozygotic than in dizy gotic twins is it possible to render likely the role of inherited factors

We must establish that neither proband studies nor twin studies have de monstrated that a major part of glaucoma cases are due to genetic factors

What can we learn from population studies?

In a number of countries large groups of the population have been screened for the frequency of ocular hypertension but these studies yield little infor mation about the aetiology of glaucoma The frequency of ocular hypertension and of glaucoma is approximately the same in most countries Also there does not seem to be any major difference in the incidence of glaucoma among men and women but already here we come up against less conformity

With respect to the composition of the glaucoma population in the different countries including the ratio of open angle to narrow angle glaucoma and the incidence of capsular glaucoma there are striking differences

It is often difficult to assess statistics from countries for which we do not know about the recruitment to eye clinics etc I shall therefore restrict myself to the Scandinavian countries

In Iceland comprehensive studies have been carried out by Sveinsson (1959)

and Bjornsson (1967) Glaucoma is common in Iceland especially among people working out of doors i e far more common among men than among women and it also runs a far more malignant course in men Less than 10 % of this glaucoma population has narrow angle glaucoma and capsular glaucoma also appears to be rare In Norway too the frequency of narrow angle glaucoma seems low In return capsular glaucoma predominates In analyses from major university clinics as well as from ophthalmic practice open angle glaucoma with pseudoexfoliations represents half or more of all cases of glaucoma In Finland large materials of patients with capsular glaucoma may be collected and the same applies at least to certain parts of Sweden On the other hand capsular glaucoma is a rare occurrence in Denmark Analysing our glaucoma material from the past 5 years in the Odense University Eye Clinic we found only one patient with capsular glaucoma About one third of our patients have had narrow angle glaucoma and this is a considerably higher frequency than in the other Scandinavian countries

The conclusions must be then that if glaucoma is an inherited disease the population of the Scandinavian countries must be of a varied genetic composition Of course there are certain differences in gene distribution but the similarities are so predominant e g in the distribution of blood groups that the differences in the glaucoma populations must be chiefly of exogenous nature I feel justified in concluding that glaucoma of old age whether open angle or narrow angle is predominantly determined by enviromental factors

This is of course not saying that there can be no question of a familial predisposition to glaucoma or that certain predisposing inherited factors do not have to be present for the disease to manifest itself
In my opinion it is not only possible but likely that this must be the case

For instance it seems to have been proved that closed angle glaucoma occurs more often in persons having shallow anterior chambers and Törnquist has demonstrated that a low depth of the chamber is to a certain extent hereditary Similar results are being obtained in studies of the Greenlandic population
Concerning glaucoma simplex a number of investigations have shown that a very large number of patients suffering from this disease give a positive corticosteroid response and that they are more often than the normal population non tasters in PTC tests

These findings tell us something about the nature of the glaucoma population but on the basis of mass screening by these tests it is not possible to decide who is going to develop glaucoma Possibly the population might be divided into different risk groups In this connection Pohjola & Horsmanheimo s study on the steroid response in patients with capsular glaucoma is of particular

interest These authors were unable to elicit the same response in patients with capsular glaucoma as in those with glaucoma simplex

Through the past thirty years we have been discussing the epidemiology of pseudoexfoliation of the lens capsule and its relation to glaucoma Weighty contributions have come not least from our Norwegian colleagues Most recently especially the investigations of Aasved (1969 1971a 1971b) are worth emphasizing Aasved has demonstrated that the very marked differences in the frequency of fibrillopathia epitheliocapsularis from country to country scarcely exist and also that the frequency of glaucoma in patients with fibrillopathia probably does not vary as much as previously assumed Lastly he found that the frequency of fibrillopathia in the glaucoma population varies considerably even within the same geographic area the frequency depending upon the patients age and the malignancy of the glaucoma

The extremely high frequencies which have previously been reported from Norway are explained mainly by the selection of the materials We have severe cases of glaucoma in Denmark too but nevertheless we rarely see exfoliations This raises the question whether fibrillopathia is a reaction pattern – an ocular change of ageing – predominantly of exogenous nature and whether its frequency in the glaucoma population is decreasing in Norway and increasing in other countries

I shall not delve further into this fascinating problem but merely emphasize that patients with pseudoexfoliations should be kept on a short leash considering that at least one third of them fairly soon develop glaucoma

Why read a paper of this nature which in fact merely reveiws previous studies and brings no essential new findings? The reason is simple Much time and much energy is expended on investigating the significance of genetic factors in the development of glaucoma whereas little interest is taken in studying possible enviromental aetiological factors Several authors among them Bjornsson have touched upon the importance of enviromental factors In Iceland the incidence is decreasing and to day it is highest in areas where people have the toughest conditions of living

With this paper I hope that I have stimulated the numerous clinics in the Scandinavian countries world famed for their interest in glaucoma and pseudo exfoliation to study the role of enviromental factors in these diseases

There must be good prospects of being able to elucidate these problems Guidance is to be had only by studying e g the occupational distribution among patients with glaucoma and the incidence of the disease among married couples – to start on something

References

Aasved H (1969) The geographical distribution of fibrillopathia epitheliocapsularis *Acta ophthal (Kbh) 47* 792–810

Aasved H (1971a) The frequency of fibrillopathia epitheliocapsularis in patients with open angle glaucoma. *Acta ophthal (Kbh) 49* 194–211

Aasved H (1971b) Mass screening for fibrillopathia epitheliocapsularis *Idem* 334–344

Bjornsson, G (1967) The primary glaucoma in Iceland *Acta ophthal (Kbh) suppl 91*

Duke Elder S (1969) *System of ophthalmology vol XI* p 402 Henry Kimpton London.

Jerndal T (1970) Goniodysgenesis and hereditary juvenile glaucoma *Acta ophthal (Kbh) suppl 107*

Pohjola S & Horsmanheimo A (1971) Topically applied corticosteroids in glaucoma capsulare *Arch Ophthal 85* 150–153

Sveinsson K (1959) Glaucoma and heredity in Iceland. *Acta ophthal (Kbh) 37* 191–198

Tornquist R (1953) Shallow anterior chamber in acute glaucoma A clinical and genetic study *Acta ophthal (Kbh) suppl 39*

Westerlund E (1947) Clinical and genetic studies on the primary glaucoma diseases *Thesis* Munksgaard København.

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Aasved H (1969) The geographica d ribution of fibrillopathia epitheliocapsularis *Acta ophthal (Kbh) 47* 792–810

Aasved H (1971a) The frequency of fibr llopathia epitheliocapsularis in patients with open angle glaucoma *Acta ophthal Kbh 49* 194–211

Aasved H (1971b) Mass screening for f b il opathia epitheliocapsularis *Idem* 334–344

Bjornsson G (1967) The primary glauco ia in Iceland *Acta ophthal (Kbh) suppl 91*

Duke Elder S (1969) *System of ophthalm l gy vol XI* p 402 Henry Kimpton London

Jerndal T (1970) Goniodysgenesis n hereditary juvenile glaucoma *Acta ophthal (Kbh) suppl 107*

Pohjola S & Horsmanheimo A (19 1) Topically applied corticosteroids in glaucoma capsulare *Arch Ophthal 85* 150–15

Sveinsson K (1959) Glaucoma and heredity in Iceland *Acta ophthal (Kbh) 37* 191–198

Tornquist R (1953) Shallow anterior chamber in acute glaucoma A clinical and genetic study *Acta ophthal (Kbh) suppl 39*

Westerlund E (1947) Clinical and genetic studies on the primary glaucoma diseases *Thesis* Munksgaard København.

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From the Eye Clinic University of Helsinki
(Head Salme Vannas)

VASCULAR CHANGES IN PSEUDOEXFOLIATION OF THE LENS CAPSULE AND CAPSULAR GLAUCOMA

A Fuorescein Angiographic and Electron Microscopic Study

BY

A VANNAS

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*From the University of Bergen
School of Medicine Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)*

TRABECULOTOMY TRABECULECTOMY AND SINUSOTOMY – SOME CLINICAL RESULTS

BY

HENRY AASVED

Trabeculotomy was carried out in 30 eyes in 3 of these combined with trabeculectomy The intraocular pressure became normalized in 23 eyes in 7 of these without post operatively medical treatment Sinusotomy was carried out in 18 eyes Satisfactory regulation of the intraocular pressure was achieved in 15 eyes in 9 of these without medical treatment
The new microsurgical methods thus seem to give a satisfactory regulation of the intraocular pressure as frequently as conventional filtration operations

Key words glaucoma – surgery – trabeculotomy – trabeculectomy – sinusotomy

The operating microscope has opened up new methods for the surgical treatment of glaucoma The last decade has seen the introduction of methods designated trabeculotomy trabeculectomy and sinusotomy The foundation for these forms of intervention lies in the theories concerning the cause of pathological increases in intraocular pressure It is usually held that the resistance to the outflow of aqueous in open angle glaucoma is chiefly localized in the tissue in the region of the inner wall of Schlemm s canal (Grant 1958 Speakman & Leeson 1962) It is also claimed that outflow may be affected intra

sclerally in other words peripherally to Schlemm's canal (Dvorak Theobald and Kirk 1956 Krasnov 1968) Corresponding to these theories one may speak of a trabecular and an intrascleral form of glaucoma (Krasnov 1968)

Theoretically trabeculotomy and/or trabeculectomy are the correct forms of *intervention in the trabecular form whereas sinusotomy would be most suitable* in the intrascleral form

These microsurgical interventions have been employed in the surgical treatment of glaucoma in the Department of Ophthalmology University of Bergen for about a year and a half

As formerly the indication for the operation has been a failure to control the condition by maximal medical treatment

Trabeculotomy has been carried out on 30 eyes in 23 patients A radial incision 3–4 mm in length was made at the junction of the cornea and the sclera A 5 mm long trabeculotom was inserted into Schlemm's canal or subsclerally to both sides of the incision and swung into the anterior chamber By this means *trabeculotomy was achieved over an area of about 10 mm In 3 of these patients* (3 eyes) trabeculectomy was carried out in addition to trabeculotomy The scleral incision was then extended a little to the sides excising the meshwork for a length of approximately 2 mm

The aperture into the anterior chamber usually resulted in a leakage of aqueous humour and the appearance of blood in the anterior chamber

On the day after operation the chamber depth was normal in all the patients and the hyphema had disappeared in most cases In 11 eyes more than 5 days elapsed before the blood in the anterior chamber disappeared Two patients

Table 1
Intraocular pressure after trabeculotomy and trabeculectomy
Obs time 5 months–16 months

Type of glaucoma	No. of eyes operated	Without med < 20 mm Hg	With medication			Operated twice
			< 20 mm Hg	20–24 mm Hg	≥ 25 mm Hg	
Simple gl	8	3	3	0	2	2
Caps gl	6	0	5	1	0	3
Pigm gl	[illegible]	0	1	0	1	1
Sec gl	14	4	7	1	2	3
Total	30	[illegible]	16	2	5	9

were left with a narrow stripe of blood intralamellarly in the peripheral area of the cornea No other complications resulted

Table 1 shows the effect of trabeculotomy and trabeculectomy on pressure regulation The results appear to be about the same in primary as in secondary glaucoma

In all a satisfactory regulation of intraocular pressure (< 20 mmHg) was achieved in 23 eyes i e 77 % 7 of these eyes being regulated without post operative medical treatment On a total of 9 eyes the operation was performed twice due to the failure of the first trabeculotomy to regulate pressure

In spite of the fact that there is increased resistance at the inner wall of Schlemm s canal it has been shown that sinusotomy has a favourable effect on intraocular pressure (Nesterov 1970)

As a relatively large number of patients still required medical treatment after trabeculotomy in order to achieve a satisfactory regulation of the intra ocular pressure sinusotomy has during the last 4 months been used as the standard method In this operation the sclera has been exposed by a relatively large limbus based conjunctival flap followed by a lamellar resection of a strip of the sclera approx 1 5 mm wide and 10 mm long immediately peripheral to the limbus from approx 11 o clock to 1 o clock. The bottom layer of the sclera is usually opened along a trabeculotom which is inserted into Schlemm s canal or subsclerally through a small radial incision As the trabecular meshwork is exposed the surgeon is able to see the transparent aqueous ooze out the intraocular pressure then falling to hypotone values although no opening has been made into the anterior chamber

Table 2
Intraocular pressure after sinustomy Obs time 1–4 months

Type of glaucoma	No of eyes operated	Without med < 20 mm Hg	With medication		
			< 20 mm Hg	20–24 mm Hg	≧ 25 mm Hg
Simple gl	9	4	4	1	0
Caps gl	3	2	1	0	0
Closed angle gl	1	1	0	0	0
Pigm gl	3	1	1	0	1
Juvenile gl	1	1	0	0	0
Haemorrh gl	1	0	0	0	1
Total	18	9	6	1	2

Sinusotomy has been carried out on a total of 18 eyes in 15 patients In 12 of these eyes simple glaucoma or capsular glaucoma had been diagnosed As Table 2 shows the intraocular pressure was satisfactorily regulated in 15 eyes in 9 eyes without post operative medical treatment Two eyes showed a post operative intraocular pressure higher than 25 mmHg In one of these in which the condition diagnosed was haemorrhagic absolute glaucoma the intraocular pressure rose to pathological levels only a few days after the operation In the other a case of glaucoma pigmentosum pathological pressure levels were reached after 2 months In the other cases in which medical treatment was required post operatively the need for this treatment revealed itself in the course of the first two weeks after the operation

There were no post operative complications and usually no uveal reaction Chamber depth was normal with the exception of one case with glaucoma pig mentosum in which peripheral iridectomy was performed simultaneously

Tonography revealed an improved out flow facility in all the 12 eyes with simple glaucoma or capsular glaucoma

Table 3 shows the frequency of satisfactory regulation of intraocular pres sure in eyes with simple glaucoma or capsular glaucoma achieved by means of trabeculotomy trabeculotomy + trabeculectomy and sinusotomy Taken as a whole the results seem very similar However most of the patients in whom tabeculotomy or trabeculotomy + trabeculectomy was performed required post operative medical treatment and all of these had to continue using Acetazol amid in addition to miotica and in some cases Adrenalin After sinusotomy local treatment was sufficient in the 5 eyes in which pressure was regulated by medication post operatively

The results of both trabeculotomy and sinusotomy appear to be approxi mately the same as in other materials (Table 4)

Table 3

Postoperative intraocular pressure < 20 mmHg in simple and capsular glaucoma

	No eyes operated	Without med No eyes	With med No eyes	
Trab tomi	11	5	6	local treatment + acetazolamid
Trab tomi + trab ectomi	3	0	2	
Sinusotomy	12	6	5	local treatment only

Table 4

Normalization of intraocular pressure in simple and capsular glaucoma in this and other studies

	Trabeculotomy				Trabeculectomy		Sinusotomy			
	Smith 1969	Harms 1969	Walker 1970	Present study	Cairns 1970	Present study	Krasnov 1970	Walker 1970	Nesterov 1970	Present study
Total No Eyes	96	84	13	11	17	3	1500	18	14	12
Normalization	[illegible]	71	8	9	[illegible]	2	80 %	14	13	11

The new forms of intervention thus seem to give a satisfactory regulation of the intraocular pressure as frequently as conventional filtration operations such as Holth s iridencleisis and Elliot s trephining It is generally agreed that the new methods involve fewer complications both in the immediate post operative period and later

Although it is too early to draw definite conclusions concerning long term results there seems to be justification for the continued use of the new micro surgical methods

Addendum November 19 ? After further 18 months observation time the results are still approximately as described in this publication

References

Cairns J E (1970) Trabeculectomy Microsurgery in glaucoma *Adv Ophthal vol 22* 143-153 Karger Basel/Munchen/New York

Dvorak Theobald G & H Q Kirk (1956) Aqueous pathways in some cases of glaucoma *Am J Ophthal 41* 11-21

Grant W M (1958) Further studies on facility of flow through the trabecular meshwork *Arch Ophthal 60* 523-533

Harms H & R Dannheim (1969) Epicritical consideration of 300 cases of trabeculotomy ab externo *Trans ophthal Soc U K 89* 491-509

Krasnov M M (1968) Externalization of Schlemm s canal (sinusotomy) in glaucoma *Brit J Ophthal 52* 157-161

Krasnov M M (1970) New Ways in Glaucoma Microsurgery Microsurgery in glaucoma *Adv Ophthal vol 22* 103-120 Karger Basel/Munchen/New York

Nesterov A P (1970) Role of the blockade of Schlemm s canal in pathogenesis of primary open angle glaucoma *Amer J Ophthal 70* 691–696
Smith R (1969) The comparison between a group of drainage operations and trabe culotomy after a follow up of five years *Trans ophthal Soc U K 89* 511–518
Speakman J S & T S Leeson (1962) Site of obstruction to aqueous outflow in chronic simple glaucoma *Brit J Ophthal 46* 321–335
Walker W M (1970) Trabeculotomy and External Fistulation of Schlemm s Canal Microsurgery in Glaucoma *Adv Ophthal vol 22* 140–142 Karger Basel/Munchen/ New York

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ADRENALIN THERAPY IN GLAUCOMA

BY

SALME VANNAS and MATTI LINKOVA

The lowering effect of adrenaline on intraocular pressure was discovered at the end of the 19th century (Darier 1891) Adrenalin was synthetised in 1904 and soon afterwards its potential for the treatment of glaucoma began to attract attention (Erdman 1914 Hamburger 1923 M Vannas 1927) In his monograph M Vannas drew attention also to the untoward effects of adrenalin therapy that had been observed at that time After the introduction of gonioscopy at the end of the 1930s it became possible to define accurately the indications for adrenalin therapy but the limitations of a more general use of adrenalin have continued to be the poor keeping quality of the drops due to oxidation and their irritating effect

Key words glaucoma – therapy – adrenalin

A new advance in adrenalin preparations came in the 1950s when the studies conducted by Goldmann (1951) Becker (1953) and Weekers (1954) resulted in drops with a better keeping quality Several preparations are in use in Finland today We selected the following as objects of close examination (Table I) In addition the domestic preparations Oftan Adrenalin® and Ocu Adre® which have a very similar composition to that of Eppy® are used Lyophrin® and Epinal® are produced by the same firm (Alcon) and Epinal is the most recent achievement Benzalconium is used as a wetting agent

Table 1
The chemical composition of the three adrenalin preparations compared

1% Eppy®		2% Lyophrin®		1% Epinal®	
Adrenalin	0 075	Adrenalin bitartr	0 15	Adrenalin	0 0 5
Acid. bor	0 150	Acid. bor	0 03	Acid bor	0 1125
Phenylhydrarg acet.	0 00015	Chlorbutol	0 0112	Benzalcon. chlorid	0 0007
Natr hydroxid.	ad pH 7 4	Natr pyrosulfis	0 015	Natr carb	ad pH 5 8
Natr pyrosulfis	0 0225	Tetracemindinatr	0 00075	Acid. ascorb	0 0375
Oxichinolin. sulf	0 000075	Aqua steril	q s ad 7.5 ml	Acetylcystein.	0 0375
Aqua steril	q s ad 7.5 ml			Methylcellulos	0 0375
				Aqua steril	q s ad 7.5 ml

and a new combination of substance (Acid ascorbic Acetylcystein) which ought to reduce oxidation is used in this compound in addition to the adrenalin borate combination. It is planned to be more stable and less irritating

The fast effects of these three preparations are evaluated in the following This study was prompted by our observation (Fig 1) that Epinal seemed to reduce intraocular pressure exceptionally effectively in some cases of very severe glaucoma.

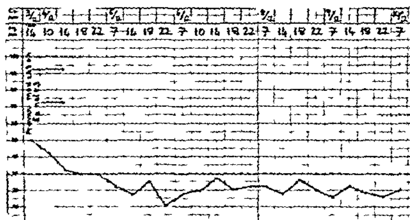


Fig 1
Additional Epinal treatment was commenced on a 20 yr old man with congenital glaucoma in R. E. Numerous previous operations and continuous glaucoma medication (6% Isoptocarpine F Piladur × 1 Glaucol ½ tabl × 3) were inadequate.

Material and Method

The material consisted of 25 eyes of 16 patients with open angle glaucoma. Fourteen of the eyes involved had recently diagnosed untreated glaucoma, five of them were glaucoma suspects only; the other patients were undergoing miotic and/or acetazolamide therapy of varying but inadequate intensity which was unchanged for the duration of the trial. Nineteen of the eyes had simple glaucoma, the others capsular glaucoma.

One drop of 1 % Eppy, 2 % Lyophrin or 1 % Epinal was instilled once a day (but only one of them on the same day). This sequence of adrenalin drops was used for 12 eyes (Table II); for the following 13 eyes of the series, however, the order of the eye drops was changed to rule out possible cumulative effect: Epinal was given first and Eppy last. An interval of one day was kept between the instillations.

Tonography was performed without any adrenalin treatment on the day preceding the experiment and again four hours after the instillation, always at the same hour. Tonography was done by the same technician during the whole series. A certified electronic tonometer of Mueller with recorder was used. The facility of outflow was calculated in the first four minutes using Friedenwald's table of 1955. Applanation pressures of the eyes were also measured prior to tonography.

The mean of the P_0 values and C values was used as a representative value for effect. The difference between the values during and before treatment was calculated for comparison.

Table II
Plan of investigation

1st day	2nd day	3rd day	4th day	5th day	6th day
No adrenalin treatment (controls)	One drop of Epinal or Eppy	–	One drop of Lyophrin	–	One drop of Eppy or Epinal
Tonography	Tonography 4 hours later	–	Tonography 4 hours later	–	Tonography 4 hours later

Table III

Effect of adrenalin eye drops on intraocular pressure (P_o) and facility of outflow (C) in 25 eyes with open angle glaucoma

	No adrenalin treatment	4 hours after the instillation of one drop of					
		Eppy	Difference	Lyophrin	Difference	Epinal	Difference
	I	II	II-I	III	III-II	IV	IV-II
P_o							
x	23 76	18 88	–4 88	18 48	–0 40	18 08	–0 80
$Se_{\bar{x}}$	1 04	0 76	0 86	0 65	0 76	0 72	0 55
C							
$\bar{x}$	0 16	0 19	0 03	0 23	0 04	0 25	0 06
$Se_{\bar{x}}$	0 014	0 017	0 013	0 016	0 016	0 017	0 011

Results

The adrenalin drops used lowered intraocular pressure (P_o) statistically significantly There was no statistically significant difference between the different preparations even though the pressure lowering effect in average was greater when Epinal was used (Table III)

All the adrenalin preparations increased C values Epinal seemed to be the most efficacious whatever the sequence of instillation The Epinal/Eppy *difference of C values was significant*

Discussion

The pressure regulatory role af adrenergic mechanisms in normal and glaucomatous eyes has been studied recently by several investigators (Langham 1967 1969 Palkama 1971) Our material consisted of eyes with varying degrees of simple and capsular glaucoma The pressure lowering effect of a drop of adrenalin was distinct The drug epinephrine is a catecholamine which is complex in its action in that it is an agonist for both α and β adrenergic receptors

The pressure lowering effect of adrenalin has been attributed to the decrease of aqueous secretion The mechanism of its decreasing effect on the secretion

of aqueous is still unclear however In addition to a direct sympathetic effect on the secretory mechanism (Weekers 1955) a change caused by the decreasing of local uveal circulation might be involved (Vannas 1927 Sears 1966)

The potential outflow increasing effect of adrenalin therapy has also aroused interest like the slow effect on the C values after half a year therapy (Ballantine & Garner 1961 Aasved 1964 Krill et al 1965 Tarkkanen & Karjalainen 1967) We demonstrated an improvement of facility of outflow four hours after the instillation of a drop of the different epinephrine preparations This concurs with the results obtained by Kronfeld (1964) and Sears (1966) Epinal® seems to be the agent that promotes facility of outflow most effectively

The fast effect of epinephrin on the outflow of aqueous might arise from the effect of α adrenergic mechanisms to the sympathetically innervated tissues The fact that the sympathetically denervated eye is more sensitive to the outflow increasing action of exogenous adrenalin speaks for an autonomous mechanism of action (Sears 1963) Barany (1962) has shown that substances that block adrenergic effect prevent the increasing of outflow facility

Summary

The effect of a drop of adrenalin on intraocular pressure (P_0) and facility of outflow (C) was studied in 25 eyes of 16 patients by administering three adrena lin preparations 1 % Eppy 2 % Lyophrin and 1 % Epinal They all lowered intraocular pressure significantly after four hours and the C values increased In the pressure reducing action of these preparations there was no significant difference though Epinal promoted facility of outflow most Further studies seem to be indicated

References

Aasved H (1964) The effect of adrenalin in glaucoma simplex *Acta ophthal (Kbh)* 42 378–386

Ballantine E J & Garner L L (1961) Improvement of the coefficient of outflow in glaucomatous eyes *Arch Ophthal* 66 314–317

Barany E H (1962) Transient increase in outflow facility after superior cervical ganglionectomy in rabbits *Arch Ophthal* 67 303–311

Becker B & Friedenwald J S (1953) Clinical aqueous outflow *Arch Ophthal* 50 557–571

Darier A (1894) Cited by H Sugar The glaucomas Kimpton London 1951 p 19

Erdmann P (1914) Subconjunctivale Injectionen von Nebennierenpraparaten *Z Augenheilk* 32 216–225

Goldmann H (1951) L origine de l hypertension oculaire dans le glaucome primitif *Ann Oculist (Paris) 184* 1086–1105

Hamburger C (1923) Experimentelle Glaukomtherapie *Med Klin 19* 1224–1225

Krill A E Newell F W & Novak M (1965) Early and long term effects of levo epinephrine *Amer J Ophthal 59* 833–839

Kronfeld P C (1964) Dose effect relationship as an aid in the evaluation of ocular hypotensive drugs *Invest Ophthal 3* 258–265

Langham M E (1967) Manometric pressure cup and tonographic procedures in the evaluation of intraocular dynamics In W Leydhecker (1966) Glaucoma Symposium Tutzing castle pp 126–150 Karger Basel

Langham M E (1969) New developments in the adrenergic pharmacology of normal and glaucomatous eyes *Trans Austr Coll Ophthal 1* 52–63

Palkama A & Uusitalo R (1971) The significance of nervous system in the control of intraocular pressure Lecture held in 1971 To be published

Sears M L (1966) The mechanism of action of adrenergic drugs in glaucoma *Invest Ophthal 5* 115–119

Sears M L & Sherk T E (1963) Supersensitivity of aqueous outflow resistance in rabbits after sympathetic denervation *Nature (London) 197* 387–388

Tarkkanen A & Karjalainen K (1967) Ueber 1 Epinephrin Behandlung bei Glaucoma simplex *Albrecht v Graefes Arch Klin exp Ophthal 172* 86–92

Vannas M (1927) Klinische Untersuchungen uber die Einwirkung des Adrenalins bei Glaukom (Thesis Univ Helsinki 1927) *Acta ophthal (Kbh) 4* 340–433

Weekers R Delmarcelle Y & Gustin J (1955) Treatment of ocular hypertension by adrenalin and diverse sympathomimetic amines *Amer J Ophthal 40* 666–672

Weekers R Prijot E Gustin J (1954) Recent advances and future prospects in the medical treatment of ocular hypertension *Brit J Ophthal 38* 742–745

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EXPERIENCE WITH KERATOPROSTHESES

BY

T I BERTELSEN and K SYVERSEN

A perforating keratoprosthesis was implanted on five patients with densely vascularized leukoma of the cornea Two of the patients ex perienced no or minimal visual improvement due to posterior segment pathology Considerable visual improvement was achieved for the other three patients Extrusion of the prosthesis frequently occured but it could be replaced without loss of the visual gain

Key words cornea keratoprosthesis corneal implant

Implantation of an keratoprosthesis is uptil now the only possible therapy for patients with such extensive corneal changes that it is impossible to obtain any visual improvement by a keratoplasty with corneal tissue

Since Stone et al s pioneer experiments with animals (1953 1955) several models of prostheses have been described that have been tried in man (Cardona 1962 1966 1969 Strampelli 1963 Dohlman 1969 Choyce 1970) Even though several hundred kerathoprosthesis operations have been performed throughout the word this ophthalmological field still is in a developmental stage The functional result can be spoiled by growth of a retroprosthetic membrane In addition extrusion of the implant detachment of the retina intraocular hemorrhage infections and eventually phtisis bulbi seem to be fairly common complications On the other hand there are reports of many cases with good results both anatomically and functionally (Castroviejo Cardona & De Voe 1969)

Material and Method

We have performed kerathoprosthesis operations only on patients with visual acuity reduced to light perception with or without light projection (Table I) and where either one or more keratoplastys failed (Nos 1 3 and 5) or an extensive scarring and vascularisation of the cornea was an obvious impediment to succesful keratoplasty (Nos 2 and 4) All our 5 patients had additional changes

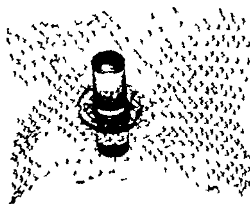


Fig 1
Keratoprosthesis with supporting plate made of warp knit nylon mesh

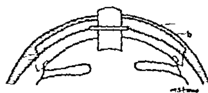


Fig 2
Keratoprosthesis in situ covered by conjunctiva or buccal mucosa (a) and supported by a full thickness corneal graft (b)

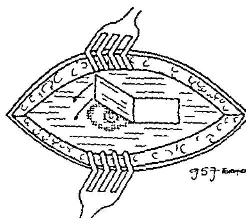


Fig 3
Keratoprosthesis is implanted between two layers of fascia lata



Fig 4
Keratoprosthesis with fascia lata ready for implantation

in the anterior segment of the eye such as symblepharon anterior synechias or cataract These changes made it necessary to perform one or more preparatory operations previous to the implantation of the keratoprosthesis The implantation was done exclusively on aphakic eyes or eyes on which a lens extraction was performed simultaneously with the implantation of the keratoprosthesis

Our keratoprosthesis is a penetrating optical cylinder made of pure methyl methacrylate with diameter 2 1 mm fitted to a supporting plate of a warp knit meshwork skirt made of monofilament nylon thread 45 mμ thick (Fig 1) The prostheses are made individually for each patient The refracting surfaces of the optical cylinder (anterior and posterior plane) are ground to suit the axial length of the eye as determined by ultrasonographic measurement The optical cylinder is made so long as to protrude ½–1 mm anterior to the tissues covering the supporting plate and 1 mm behind the posterior surface of the recipient cornea in order to prevent overgrowth from the surrounding tissues The total length of the optical cylinder has been 4–6 mm Two versions of the operation have been performed

1 A superficial keratectomia is done Hence the supporting meshwork skirt is trimmed to a diameter of approximately 15 mm in order to cover not only the cornea but also a part of the adjacent sclera The prosthesis is then implanted and the supporting skirt covered by a fresh full thickness corneal graft Both the optical cylinder and the graft are covered by a conjunctival flap or a

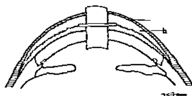


Fig 5
Keratoprosthesis in situ covered by conjunctiva or buccal mucosa (a) The nylon mesh work skirt is imbedded in a fascia lata autograft (b)



Fig 6
Patient No 2 Rockblasting accident 1954
O D L Prj O S No L Prc

thin layer of buccal mucosal autograft if sufficient conjunctiva is not available After 2–3 weeks an opening is made in the conjunctiva or buccal mucosa anterior to the optical cylinder (Fig 2)

2 The prosthesis is preliminarily implanted in one of the patients thighs between a double layer of fascia lata (Fig 3) 2–3 months later when the supporting meshwork skirt has been firmly anchored in the fascia the prosthesis with a piece of the surrounding fascia lata is removed (Fig 4) and implanted in the cornea subsequent to a superficial keratectomia The optical cylinder and the fascia is then covered with conjunctiva or buccal mucosa which is opened after 2–3 weeks (Fig 5)

All our patients were primarily operated with the first modification Patient No 1 (Table I) who suffered recurrent extrusions was ultimately operated with modification No 2

Results

Initially there was an anatomically satisfactory result in all the five patients The postoperative reaction was negligible and the prostheses were well fixed However necrosis of the corneal graft overlying the supporting plate occured in 3 of the patients 8–20 months after the implantation The necrosis always originated in the tissue surrounding the anterior projection of the optical cylinder and extended peripherically in the course of several weeks As the covering graft slowly eroded the prosthesis gradually moved forward and a membrane formed behind the optical cylinder closing the aperture in the recipient cornea Replacement of the prosthesis in these cases could be performed without great difficulty and without loss of the gained vision

The two patients who previously to the operation only had light perception showed no objective improvement of vision The three patients who prior to the operation had light projection showed an improvement of vision to respectively 6/6 F C $1/2$ m and F C $2^{1}/_{2}$ m

For further details regarding the patients see Table I

Comments

Due to the difficulty of estimating the thickness of the cornea and the supporting tissue in these eyes several prostheses with varying length of the anterior and posterior protrusion should be available during the operation

Table I

Subsequent to the completion of this paper patient No 1 suffered extrusion of the prosthesis 11 months after implantation

Pat No	Sex Age	Cause of visual loss	Visual acuity before operation O D	O S	Time of first implantation	Visual acuity on operated eye Nov -72 O D	O S	Comments
1	5[illegible] ♂	Burns by melted iron 1958	Anophth	L Prj	Nov -68		6/6	Prosth replaced one time because of posterior membrane and three times because of impending extrusion
2	60 ♂	Rockblasting accident 1954	L Prj	No L Pre	April -70	F C ½ m		Prosth replaced after 19 months because of impending extrusion Travel vision
3	76 ♂	Congenital syphilis	L Pre	L Pre	July -70	L Pre		Chorioretinal scars No visual improvement [illegible] Prosthesis removed after 14 months
4	74 ♀	Sympathetic ophthalmia 1904	L Pre	L Pre	Febr -71	L Pre		Prosth replaced after 20 months because of extrusion Chorioretinal scars Can see the light better
5	5[illegible] ♂	Sulphuric acid burns 1970	Anophth	L Prj	May -72		F C 2½ m	Travel vision

L Pre = Light perception L Prj = Light projection F C = Finger counting

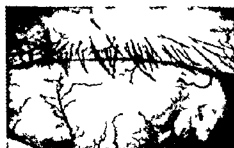


Fig 7
Patient No 2 O D before implantation of keratoprosthesis



Fig 8
Patient No [illegible] O D 2 months after implantation of keratoprosthesis

The necrosis of the supporting corneal graft always proceeded gradually and with little or no inflammatory reaction It would seem to us that we were dealing with an aseptic necrosis rather than an immunological reaction Development of a retroprosthetic membrane would indicate the necessity of implanting another prosthesis which extends further into the anterior chamber An anterior membrane though easily removed increases the danger of necrosis of the vulnerable tissue surrounding the anterior projection of the optical cylinder Intraocular hemorrhage retinal detachment or infection were not found in any of the cases All the three patients who achieved a substantial improvement of vision require good illumination to profit from their potential vision When evaluating the results of the operation one must take into consideration that none of the patients had better vision than light projection preoperatively and that no other treatment could have resulted in a corresponding improvement of vision

Acknowledgment

We are indepted to Nils Teigland ophthalmic optician for his great interest and effort in producing the keratoprostheses

References

Cardona H (19[illegible]) Kerat[illegible] thesis *Am J Ophthal* [illegible] 284–291

Cardona H (196[illegible]) [illegible] terior mushroom keratoprostheses *Am J Ophthal* *61* 498–504

Cardona H (1969) Mushroom transcorneal keratoprosthesis (Bolt and nut) *Am J Ophthal 68* 604–619

Castroviejo R, Cardona H & De Voe A G (1969) Present status of prosthokeratoplasty *Am J Ophthal 68* 613–625

Choyce D P (1970) Perforating kerato prosthesis The Choyce Mk II (1967) 2 piece perforating kerato prosthesis *Trans Ophth Soc U K 90* 23–29

Dohlman Cl H Webster R G Biswas S K & Refojo M F (1969) Protheses cornéennes a double plaque maintenues a l aide d adhesifs chirurgicaux *Arch Opht 29* 169–174

Stone W Jr & Herbert E (1953) Experimental study of plastic material as replacement for the cornea A preliminary report *Am J Ophthal 36* 168–173

Stone W Jr (1955) Study of patency of openings in corneas anterior to interlamellar plastic artificial discs *Am J Ophthal 39* 185–195

Strampelli B (1963) Osteo odontocheratoprotesi *Ann Ottalmol Clin Ocul 89* 1039–1044

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CLINICAL AND HISTOLOGICAL FINDINGS IN CRYSTALLINE CORNEAL DYSTROPHY

BY

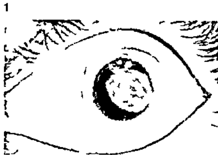
K GROP

Crystalline corneal dystrophy is characterized by bilateral central corneal opacity consisting of subepithelial needle like crystals The disease is hereditary transmitted by autosomal dominance The opacity may be observed already during infancy or is possibly congenital It progresses very slowly and as a rule a normal or good visual acuity is preserved up to the age of 40–50 years The sensibility is slightly reduced The cornea is not vascularized The patients have no complaints

The opacity may vary considerably both in size and appearance in the various patients but as a rule it is symmetrical Fig 1 shows a rather thin patch where the individual crystals may be observed In Fig 2 the opacity is larger and also denser causing an impairment of vision to 0 6 The opacity is always sharply delimited The crystals are white or may at times shimmer in bright colours The dystrophy may also be circular or consist of several small separate patches

This condition was described by Schnyder in 1929 and in 1939 who was erroneously thought to be the first to mention it but the cases described in 1924 by Went and Wibaut were the same disease Subsequently it has been described in about 30 papers and a total of approx 70 cases are by now on record The ordinary clinical picture and the dominant heredity have been elucidated Histological investigations have been carried out on pieces of corneae and it has been concluded that the crystals probably consist of cholesterol

1



2



Fig 1

Crystalline Corneal Dystrophy 18 year old male with central rather thin patch where the individual crystal may be observed. In both corneae of the patient s brother ap peared a very faint diffuse stromal opacification centrally ringshaped with 4 mm diameter A faint arcus senilis was present No crystals were observed.

Fig 2

Crystalline Corneal Dystrophy 82 year old man Diffuse corneal opacification without crystals Pronounced arcus senilis This eye was histologically examined (Fig 6 7 8 9)

My own series comprises 17 cases from the same family domiciled in central Finland The dominant heredity is clearly apparent The youngest patient is 7 years of age and the oldest 82 13 are males and 4 females

The results support previous studies The visual acuity has remained normal with a few exceptions up to the age of 50–60 corneal sensibility is slightly reduced and the cornea is not vascularized The patients have no ocular com plaints

Previous investigations have shown that the disease is slowly progressing but according to the present study it also changes in nature with advancing age During childhood and adolescence the cornea is quite clear except for the crystalline opacity The opacity slowly progresses up to the age of about 30 At about 20 years of age there appears also a diffuse peripheral arcus senilis In all patients over 20 years of age a total of 14 an arcus senilis was present exactly like a normal arcus senilis At about 30 years of age a similar diffuse opacity may be seen in the central and intermediate part of the cornea It is amorphous and comprises all layers of the stroma In 7 out of the 8 patients who are over 40 years of age this stromal opacity is accentuated to a ring about 4 mm in diameter in the centre of the cornea

It is my definite impression that the crystals decrease in number and size after the age of 30–40 and that the progression of the disease is due to an

3



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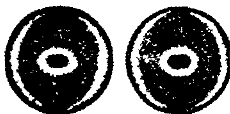


Fig 3

Crystalline Corneal Dystrophy 49 year old man Right eye Central patch with sub epithelial needlelike crystals and diffuse stromal opacification Pronounced arcus senilis In the left eye was observed central stromal opacification and arcus senilis but no crystals

Fig 4

Crystalline Corneal Dystrophy Case no 4 from Sysi s publication at the age of 4 years *Central crystalline ring*

increasing density of the diffuse opacity In particular the arcus senilis is very striking in the oldest patients and at the time they exhibit a few small scattered crystals

As already mentioned the dystrophy is generally symmetrical but in the 48 year old man the left eye exhibited typical crystalline dystrophy as well as *a faint diffuse central ring of the appearance described above On the other* hand the right eye housed no crystals but only a fairly severe central stromal opacity In my opinion this finding supports my view that the crystalline opacity is gradually replaced by or passes into a diffuse opacity In the present case the development in the right eye had progressed somewhat farther

The same changes with advancing age I found when examining two of the four cases published by Sysi in 1950 Sysi s Case 4 may be seen on the illustration from his publication At that time the patient was 4 years of age There *is an arcuate crystalline opacity The periphery is said to be rather indistinct* At the age of 23 the opacity is in the form of a round patch and at the age of 29 there is a dense disc as well as a marked arcus senilis On the other hand I could not detect any central diffuse opacity The photos clearly show that the crystalline opacity has increased in extent from the age of 4 to 29

Fig 2 shows the eye of an 82 year old man The picture was taken a few days before he died of pneumonia I had the occasion to have this eyeball examined histologically by Dr Merenmies of the University Eye Clinic Hel

5



6

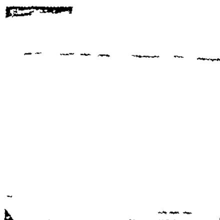


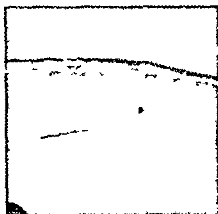
Fig 5

Crystalline Corneal Dystrophy The same case as presented in Fig 4 at the age of 29 years Central crystalline patch and pronounced arcus senilis

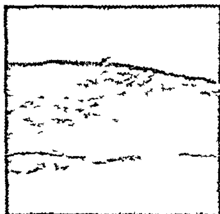
Fig 6

Crystal Corneal Dystrophy Histological section of cornea from the eye presented in Fig 2 Bowman s membrane broken down in places with replacing cicatricial tissue in which are clefts where crystals have become detached in the course of preparation

7



8



Fig

Crystalline Corneal Dystrophy Same eye as presented in Fig 6 Frozen section of the cornea photographed in polarized light In the middle of the cornea subepithelial birefrigent crystals are observed

Fig 8

Crystalline Corneal Dystrophy Same eye as presented in Fig 6 Frozen section photographed in polarized light Close to limbus crystals appear in the deeper layers of the corneal stroma

sinki The examination revealed that in places Bowman's membrane was broken down and replaced by cicatricial tissue (Fig 6) In the cicatricial tissue there are clefts left by the crystals which had become detached in the course of preparation

Fig 7 shows a frozen section photographed in polarized light In the middle there are birefringent crystals only in a subepithelial situation Close to the limbus they occur only down through half the stroma (Fig 8) With a phase contrast technique the majority of the crystals are seen to be of a needle like shape At higher magnification needle like crystals are distinctly apparent Examination of other parts of the eyeball disclosed birefringent crystals also in the anterior parts of the sclera – but only in its deeper layers (Fig 9) To my knowledge this has not been demonstrated so far as previously there has not been access to a whole eyeball The finding shows that the dystrophy is not restricted merely to the cornea and that it is reasonable to assume that the metabolic disturbance underlying the disease also causes changes in other sites although such changes have not yet been demonstrated In the endeavour to elucidate this problem in more detail the blood chemistry in these cases has been thoroughly analysed However the results are not yet available It may be imagined even that the dystrophy gene is coupled to some known blood group and therefore a comprehensive blood grouping is being carried out but these results are also not available as yet The studies are being continued

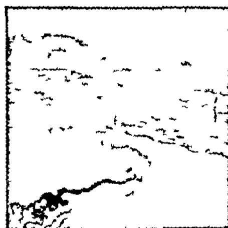


Fig 9

Crystalline Corneal Dystrophy Same eye as presented in Fig 6 Frozen section photographed in polarized light Crystals occur in the deeper layers of the anterior sclera

References

Axenfeld T (1930) Dystrophien des Korneaparenchyms *Klin Mbl Augenheilk* 85 493

Bonnet P Paufique L & Bonamour G (1934) Cristaux de cholesterine de au centre de la cornea avec gerontoxon *Bull Soc Ophtal (Paris)* 275

Delleman J W & Winkelman J E (1968) Degeneratio corneae cristallina hereditaria *Ophthalmologica 155* No 5

de Schweinitz & Cowan (1932) An unusual corneal lesion probably congenital and familial in character A slitlamp study *Tr Am Ophth soc 30* 218

Fry W E & Pickett W E (1950) Crystalline dystrophy of the cornea *Trans Amer ophthal Soc 58* 220-227

Schnyder W F (1927 1929) Mitteilung uber einen neuen Typus von familiarer Hornhauterkrankung *Schwei med Wschr 59* 559

Schnyder W F (1939) Scheibenformige Kristallenlagerungen in der Hornhautmitte als Erbleiben *Klin Mbl Augenheilk 103* 494

Sysi R (1950) Xanthoma corneae as hereditary dystrophy *Brit J Ophthal 34* 369

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Reykjavik Iceland 20–24 June 1971

From Oslo University Eye Department
(Head Professor dr med Thore Lie Thomassen)
and Neurosurgical Department
(Head Professor dr med Tormod Hauge)
Rikshospitalet Oslo Norway

DYNAMIC TONOMETRY IN CAROTID OCCLUSIVE DISEASE

BY

IVAR HØRVEN HELGE NORNES PER SYRDALEN and
ASBJORN M TØNJUM

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*Das Schrifttum über Diabetes
und Auge ist unübersehbar*
Velhagen

OPHTHALMOLOGICAL INVOLVEMENTS IN DIABETES

An Introduction

BY

HOLGER EHLERS

This year we can celebrate a Golden Jubilee. It was in 1921 that the Canadian physiologists MacLeod, Banting and Best succeeded in producing insulin. The Nobel prize was a well deserved recognition.

Industrial production of insulin depends on farming and slaughtering and thus Denmark became an insulin producing country. In 1932 Nordisk Insulin Laboratorium established its hospital for diabetics named after the Danish anatomist Niels Steensen (Steno) who discovered the glands. This hospital was founded by H. C. Hagedorn but is now under the leadership of Jacob Poulsen. Nearly as long as the Niels Steensen Hospital has existed its ophthalmological cases have been entrusted to my care. What I shall record now are some experiences from my work there during these many years.

Diabetic manifestations in the eye

1) External	6) Tension
2) Refraction	7) Optic nerve
3) Cataract	8) Motility
4) Pigments	9) Vitreous
5) Iris	10) Retina

The purpose of this introduction must be to give a survey of the topic to be discussed afterwards in more details by others First I shall outline the aspects of ophthalmology concerned with the diabetic manifestations

External manifestations During examination of the outer eye – best of course with the slit lamp and microscope – changes in the limbal vessels are very often seen as microaneurysms small varicosities obliterations of the palisade vessels deposits such as pinguecula fine wrinkles at the margin of the cornea etc. Such changes may also be found in patients with cardiac or renal diseases in hypertonics, or in healthy persons presenting for ophthalmological examination only for prescription of glasses The outer eye seems so exposed to many fortuitous influences "ab externo" that many – undoubtedly diabetic – changes are difficult to estimate

Refractive changes are among the earliest and most common ocular signs of diabetes After questioning a large number of diabetics I may state that nearly half seemed well acquainted with this transitory refractive trouble On the other hand a patient seldom comes to refractometry during the transitory stage The changes in refraction – hypermetropic as well as myopic – seldom reach a high degree as a rule only a few dioptres Similar transitory refractory changes are seen during treatment with diuretics and may also be found in a state of emaciation (V A. Jensen) Diet and diuretic factors therefore must be fundamentally involved in the pathogenesis but how? Many authors presume that the transitory refractive changes are due to changes in the lens An important argument for this assumption is that diabetics operated on for unilateral cataract may develop transitory hypermetropia in the unoperated eye but not in the aphakic eye However convincing this experience may appear it proves only that the curved surfaces of the lens are necessary for producing the refractive changes but does not tell us which side of the curved surface is affected by these changes

Cataract may be due to so many causes that the mere coincidence of cataract and diabetes does not prove the existence of a diabetic cataract The reason why even in the past century a diabetic cataract could nevertheless be recognized was the common occurrence of bilateral juvenile, progressive cataracts in diabetics in those times I still remember the smell of acetone in my nose so many years after when I recall my examinations of these young diabetics Nowadays the diabetes has generally been diagnosed before the ophthalmological examination, and bilateral juvenile progressive cataracts in diabetics have not increased in frequency as have so many other manifestations in the eyes of diabetics. For senile or presenile cataracts too diabetes is a predisposing factor

This is proved merely by the fact that routine examinations of the urines of patients in an eye department disclose sugar more often in patients admitted for cataract extraction than in other patients It has often been tried to characterize a special diabetic cataract with vacuoles small patches pearl gloss etc I myself dare not undertake such a morphological differentiation of a cataract as diabetic

Pigmentopathy is not uncommonly encountered during intraocular operations on diabetics Fine particles of pigment may have broken loose staining the aqueous brownish Even without operation we sometimes observe brown particles in the aqueous of diabetics especially after exaggerated movements of the iris On diascleral illumination of the eye some diabetics exhibit many small pellucid patches in the iris These patches represent sites where the pigment is lacking and light is passing through V A Jensen & Lundbæk have described an ophthalmoscopically visible diabetic pigmentopathy with pigment granules in the macula

Iridopathy A certain stiffness or sluggishness of the iris is often observed in diabetics The light reflex of the pupil may be weak or even abolished The movement of their iris may be slow and drugs acting on the iris may give diminished reactions Ohrt to whose book I refer found diminished reflex to light in one third of his diabetics on pupillographic examination Iritis may be seen in diabetics perhaps rather more often than in non diabetics but the typical iridopathia is the rubeosis of the iris In such cases the iris shows numerous red dilated blood vessels It is a late complication in diabetes seen especially in eye with proliferating retinopathy and hypertension As a rule these cases end as haemorrhagic glaucoma dolorosum Although I have seen regression in some cases of rubeosis iridis these cases must be considered as the most severe diabetic involvements of the eyes and the final outcome is as a rule enucleation

Intraocular tension Except for the consecutive glaucomas in diabetics the intraocular tension is usually a little lower than in normals That the eyes of patients in diabetic coma may feel even soft is an old observation from the times before insulin treatment was started In normals moderate injections of insulin are ordinarily followed by a slight reduction of intraocular tension During a certain period Gregersen measured the intraocular tension in all patients referred for examination from the Niels Steensen Hospital On an average the tension in diabetics was a few mmHg lower than in the control group of normals Others however have reported the opposite findings In spite of an extensive literature concerning diabetes and glaucoma I agree with Velhagen that it is schwer ein System hineinzubringen

Optic neuritis with impaired visual acuity and central scotoma but without retinopathy was formerly not uncommon in obese elderly diabetics The optic neuritis was thought to be toxic I recall some restaurant keepers with this disease probably caused by a combination of drinking and poorly managed diabetes Abstinence and an increased dose of insulin improved the vision Such cases have now become rare I have not met any for quite a number of years

Motility Diabetic palsies of the eye muscles play rather an impressive role in the literature on diabetic involvements of the eyes The oculomotor muscles may often be affected but pareses of the trochlear and abducent nerves are also on record I do not know why but among the many diabetics I have seen during all these years I remember only a very few cases In my experience pareses of the extraocular muscles are extremely rare

Vitreopathy is an early phenomenon In the ophthalmoscope it presents an impressive and changing picture of sparkling light reflexes in the fundus The normal and well known reflections in the fovea around the macula and along the vessels change and new patterns are formed The fundus may be seen as through a piece of transparent but crumpled cellophane or poly ethylene These reflections are difficult to photograph With the slit lamp and the Hruby lens the vitreous will be seen to be more or less detached deranged liquified or even collapsed Preretinal or perhaps better retrovitreal spaces are formed Haemorrhages from the retinal vessels may fill these spaces ap pearing as limited red patches between the retina and vitreous If red cell sedimentation occurs "halfmoons are formed If the haemorrhage breaks through to the interior of the liquefied vitreous the papilla will be obscured by more or less diffuse vitreous haemorrhages so called juvenile recurrent vitreous haemorrhages If the consistency of the vitreous is preserved to some degree the haemorrhages may stand out as stripes somewhat like a pennant in the vitreous

Retinopathy It is not surprising that diabetic involvements of the retina have commanded the early and intense interest of ophthalmologists Instead of attempting a detailed description of all these different ophthalmological pictures I shall demonstrate a series of retinal photographs including some of Hans Walther Larsen s To bring any system into all these various pictures is not easy Often a distinction is made between simplex cases" and proliferative cases but this is not a good distinction since many simplex cases especially in young persons represent only a non proliferating precursor phase of pro liferating retinopathy After many years of practice I have settled on the following classification

Retinopathy in diabetics

1) Arteriosclerotic
2) Phlebectatic
3) Proliferative
4) Penetrating to vitreous
5) Compound types

The *arteriosclerotic* type is very common in middle aged diabetics there is no preretinal proliferation of vessels Complete blindness is rare

The *phlebectatic* type is seen in young persons It may remain stationary for a long time or even regress but often ends as proliferative

The *proliferative* type has got less common but is very dangerous

The *penetrating* type may cause sudden blindness

The *compound* cases run a dubious course

Time to-day permits only some stray comments

Vascular changes from the smallest microaneurysms to big tufts of vessels are – though not pathognomonic of diabetes – nevertheless remarkable phe nomena *New formed vessels – in the form of collaterals rete mirabile ana* stomoses etc – may be intraretinal or preretinal (retrovitreal) While the intraretinal formations of vessels are very common in vascular diseases of the retina the preretinal formations occur only in diabetes and in a few others diseases viz retrolental fibroplasia Eales disease haemochromatosis Walden strom s macroglobulinaemia (fundus paraproteinaemicus) and finally in pro liferative retinitis after infections or lesions of the vitreous Furthermore it is well to bear in mind the vascular changes after excessive ACTH medication and the disappearance of the vessels in Simmonds disease and after hypophy sectomy

Extensive research has been devoted to these vascular proliferations It would be of great interest to know why the vessels normally avoid the vitreous In embryonic life the extensive vascular system in the primary vitreous completely disappears as soon as the secondary vitreous is formed Vessels in the body are like grass They develop everywhere in the tissues except where their growth is undesired e g in the cornea lens and vitreous

Myopia and retinopathy A curious and interesting observation now con firmed by many other clinicians is that retinopathy is less common in myopic than in other diabetics No explanation can be given at present but the obser

vation opens up interesting possibilities Either the retinopathy may be hampered by local factors in the myopic eye or the myopia itself has a more universal cause and may be a symptom of some metabolic disease in the tissues

Fluorescence angiography has been rendered possible by eminent instrumentarium It gives us information on the circulation through the retinal vessels and may disclose leakages in the vessels Some slides from the University Eye Clinic in Århus will be demonstrated Fluorescence angiography is a very promising method of examination

Among *therapeutic methods* tried in diabetic retinopathy the following may be mentioned Avoidance of visual strain X ray treatment systemic treatment with anticoagulants diascleral diathermy retrobulbar injections photocoagulations laser treatment hypophysectomy and other operations on the hypophysis Nevertheless it must not be forgotten that prevention is better than cure Instead of trying to limit the retinopathy by more or less mutilating treatments it would be better to prevent its occurrence In my opinion there can be no doubt that careful systemic treatment of diabetics is of immense significance As the retinopathy is a tardive involvement we generally have several years at our disposal

If finally we try to view in retrospect these 50 years that have elapsed since insulin was introduced it must be admitted that an exaggerated confidence in the new treatment unfortunately brought along with it the free diet During the latter half of the thirties a multitude of retinopathies appeared – so many that sometimes it was said Before the time of insulin the patients died of their diabetes now they get blind However it must be realized that all types of retinopathy were known and had been described already before the advent of insulin but the frequency of the different types has changed Furthermore the age of patients with retinopathy has changed and thus any evaluation of the situation was difficult

The last 20 years have again changed the situation If as in the Niels Steensen Hospital we keep the patients on a strict diet control their insulin requirement at short intervals recommend plenty of exercise and protect them from infections and immunological reactions diabetic complications will decrease Less than 10 % of all diabetics die blind (Jac Poulsen 1967) To day the most common type of retinopathy is arteriosclerotic In the Niels Steensen Hospital new cases of proliferative retinopathy did not even reach a frequency of 1 in 1000 among all diabetics controlled during the year 1970

Looking ahead we can state that much promising research in diabetes is being performed The metabolism of sugar may be followed biochemically

step by step By refined methods the activity of insulin may be studied in the tissues It is to be hoped that we may look forward to the day when diabetic retinopathy has been conquered Presumably this will happen as earlier in the history of blindness – due to smallpox keratomalacia ophthalmoblen *norrhoea syphilis pneumococcal infections after loss of blood etc* – *and a* great deal of the honour will be due to disciplines other than ophthalmology

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PREGNANCY AND DIABETIC RETINOPATHY

BY

P E WALINDER B WADMAN L. ANDERSSON and B SVEDBERGH

Summary

There have been reports of a few cases in which diabetic retinopathy has been aggravated during pregnancy Some of the patients have improved after delivery but in some the visual impairment has been lasting

In the present study 24 diabetics were followed during and after pregnancy having frequent checks of the blood sugar and fundus The treatment of the diabetes aimed at a blood sugar below 100 mg/100 ml The fundus was examined in the ophthalmoscope and photographed In some cases fluorescein angiography was performed The patients ranged in age from 17 to 37 years and the duration of their diabetes was from 0-24 years Two had mild toxaemia of pregnancy One had an early spontaneous abortion and one a stillbirth In 16 of the 24 patients diabetic retinopathy was diagnosed of the proliferative type in 3 Five exhibited unmistakable progression of the retinopathy during pregnancy Two of them had mild toxaemia of pregnancy Of the remaining 3 patients 2 developed proliferative retinopathy In all 5 cases the changes regressed partially after delivery

Two of the 3 patients who got worse (without having toxaemia) exhibited considerably higher triglyceride values than the mean values for the entire series towards the termination of pregnancy On the other hand there was no difference in the cholesterol levels

Key words diabetes pregnancy – retinopathy

The study has shown that in spite of very careful supervision of pregnant diabetics the retinopathy may get worse in some cases The results confirm previous reports that patients having retinopathy at the commencement of a pregnancy or having diabetes of long duration run the greatest risk of exacerbation and that the prognosis is most serious for patients with proliferative retinopathy

Discussion

Gunnar von Bahr Fluorescein angiographic studies have shown arrested circulation in limited capillary areas as the earliest sign of retinopathy It has also been maintained that increased platelet aggregation was a factor in the vascular occlusion It is reasonable to assume that the increased tendency to agglutination of the red blood cells expressed in the elevated erythrocyte sedimentation rate plays a pathogenetic role in retinopathy It is remarkable that diabetic retinopathy gets worse during infections and pregnancy conditions in which the sedimentation rate is elevated and that a retinopathy similar to the diabetic one occurs in macroglobulinaemia and in myelomatosis which are also associated with an increased tendency to blood cell agglutination These phenomena warrant further study

P Svane Knudsen As is well known it is difficult to control pregnant diabetics during the last part of the pregnancy because of the increasing foetal insulin production I want to ask Dr Wålinder whether it was also difficult to control the diabetes in the cases in which the retinopathy progressed

P E Wålinder The patients with progressive retinopathy were not more difficult to control as regards the bloodsugar but the rise in triglycerides in some of them may indicate that they had a more labile diabetes than the others

Reference

F I Caird A Pirie & T G Ramsell (1969) Diabetes and the Eye Oxford and Edinburgh Blackwell

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l c and the Clinic of Internal Medicine
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P AND DIABETIC RETINOPATHY

BY

P E \ /AN L ANDERSSON and B SVEDBERGH

Summary

There have been re ey cases in which diabetic retinopathy has been aggravated durin, p some of the patients have improved after delivery but in some the rment has been lasting

In the present study et es were followed during and after pregnancy having frequent checks blood sugar and fundus The treatment of the diabetes aimed at a bloc ar below 100 mg/100 ml The fundus was examined in the ophthalmos pe and photographed In some cases fluorescein angiography was performed The patients ranged in age from 17 to 3 years and the duration of their diabetes was from 0–24 years Two had mild toxaemia of pregnancy One had an early spontaneous abortion and one a stillbirth In 16 of the 24 patients diabetic retinopathy was diagnosed of the proliferative type in 3 Five exhibited unmistakable progression of the retinopathy durin pregnancy Two of them had mild toxaemia of pregnancy Of the remainin 3 patients 2 developed proliferative retinopathy In all 5 cases the changes regressed partially after delivery

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Key words diabetes – pregnancy – retinopahy

Table 1

Patient code	Sex	Age	Duration of diabetes (years)	Remarks concerning specimens	Clinical observations in iris	Pigment granule changes
A	male	25	7	enucleation owing to *uveal melanoma*	mild atrophy of pigment *epithelium*	only scattered changes
B	male	28	2	iris biopsy specimen excised at cataract operation	mild atrophy of pigment epithelium	scattered changes
C	female	34	14	iris biopsy specimen excised at cataract operation	mild atrophy of pigment epithelium	fairly extensive changes
D	female	32	24	*enucleation owing to* intractable haemorrhagic glaucoma	*grave atrophy of pigment* epithelium	extensive changes

All the specimens obtained were immediately fixed in cacodylate buffered 4 % glutaraldehyde Then followed postfixation in osmium tetroxide and after dehydration embedding in araldite

From patient A iris tissue was taken for glycogen digestion the glutaralde hyde fixed block having been incubated in amylase (2 mg/ml) for 15–30 minutes at 37° (Thornell 1969) prior to osmium fixation

Further iris tissue from the same patient was subjected to ribonuclease digestion Control specimens were in both cases incubated without addition of enzyme

A JEM T 7 electron microscope was used for electron microscopy In ad dition semifine sections were subjected to light microscopy

In the present communication only fine structural changes will be commented on and even only in as far as such changes served to distinguish the pigment

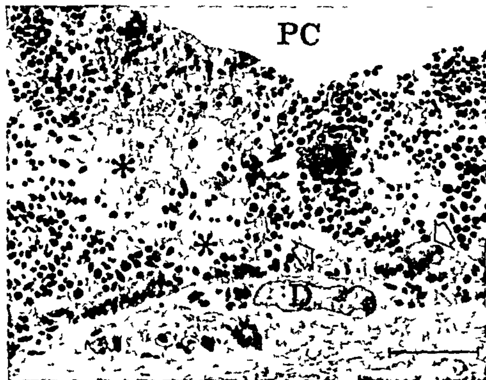


Fig 1

Survey of pigment epithelium in diabetic patient Intracellular glycogen accumulation is marked by asterisks and intercellular glycogen accumulation by arrows PC posterior chamber N nucleus in pigment epithelium and D nucleus in dilatator muscle cell 10 microns indicated

epithelium of diabetics from that of 16 non diabetic controls (J Hvidberg Hansen 1971)

That which in the first place attracted attention was observation of some changes in the pigment granules (Figs 3 and 4) Such changes have not been noticed on examination of non diabetics though the pigment configuration displays certain variations The changes which might create the illusion of disintegration of the pigment granules were noticed in all four diabetics though in different degrees cf Table I A fairly small proportion only of the pigment granules had changed These often lay in groups typically situated close to the cell boundary bordering on the posterior chamber Within the circumference of the disintegrated granules the cytoplasm was found to contain electron opaque particles which seemed to correspond to the contents of the pigment granules These particles remained uninfluenced by amylase and ribonuclease

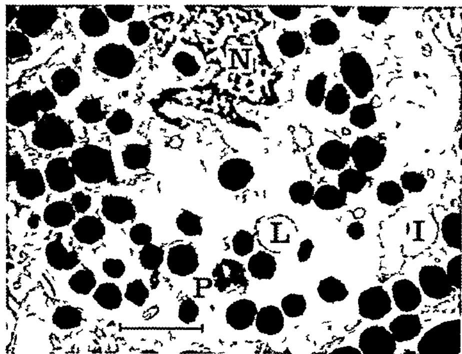


Fig 2

Section of pigment epithelium after amylase treatment. Large areas between the pigment granules and the intercellular spaces (F) are empty unlike the conditions without amylase treatment P marks an abnormal pigment granule and L a droplet of lipid. 3 microns indicated

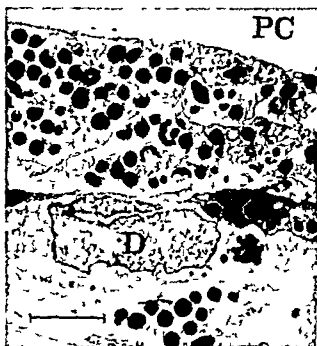


Fig 3

Survey of pigment epithelium with abnormal pigment granules in a diabetic A thickened basal membrane is seen towards the posterior chamber (PC) Nucleus in dilatator muscle marked D 4 microns indicated

Note that under the membrane enclosing the normal configurated pigment granules we find particles resembling glycogen particles which become de composed by amylase but not by ribonuclease (Fig 5) Such were also observed in non diabetics and there seems to be neither a quantitative nor a qualitative difference within this special field

A great number of glycogen like granules was found in the pigment epithe lium from the four diabetics Be it mentioned that amylase decomposable glycogen also is present in non diabetics though in smaller amounts than those observed in the diabetics

Similarly as in non diabetics the glycogen granules were located both intra and intercellularly (Fig 1) The results of the enzymatic study bore out the presumption of glycogen content in and between the epithelial cells (Figs 2 and 5)

None of the diabetic patients presented any pronounced vacuolisation in the cells

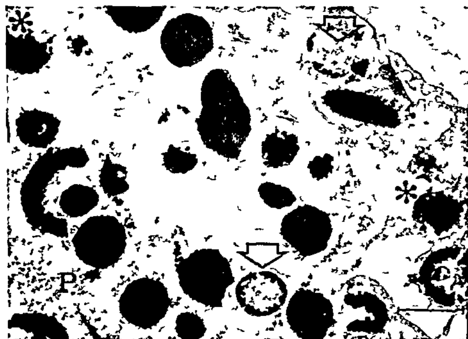


Fig 4

Abnormal pigment granules (segment of Fig 3) Some granules (arrow) seem to be in a state of disintegration from within while others give the impression of being in a state of erosion from without (asterisk) In the cytoplasm electrondense irregular particles are visible which seem to be pigment debris (P) 1 micron indicated

Yanoff Fine & Berkow (1970) subjected an autopsy material to an electron microscopical study to disclose changes in the pigment epithelial cells on the posterior surface of the iris in relation to diabetes Glycogen was found in ill defined nearly empty vacuoles in the cells and in addition a non identified material The appearance of the pigment granules has not been described in detail Hollenberg Nayyar & Burt (1968) and Hollenberg & Burt (1969) who examined the retinal pigment epithelium of rats in the presence of diabetes likewise made no mention of pigment granule changes

Feeny Grieshaber & Hogan (1965) have studied human ocular pigment and described individual variations in appearance of the pigment granules of iris epithelium They found among other things a fairly loose configuration in a single case Similar variations were also noticed in normal series but changes like those illustrated were not observed

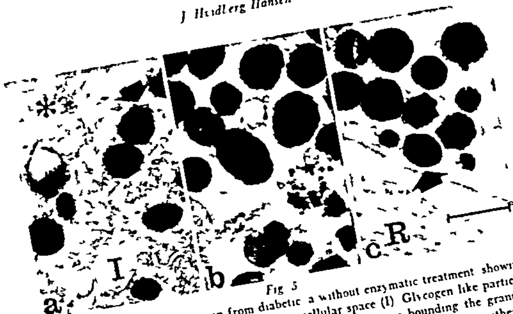


Fig 5

Pigmented epithelial cell section from diabetic a without enzymatic treatment showing glycogen like granules at asterisk and in intercellular space (I) Glycogen like particles are seen at the arrow These are located under the membrane bounding the granule b shows the conditions after amylase digestion Glycogen granules are seen neither in the cytoplasm nor in relation to the pigment granules c illustrates the conditions after ribonuclease treatment The preserved glycogen granules are here situated as in a Note especially at the arrow particles under the membrane bounding the pigment granule R represents rough endoplasmatic reticulm deprived of ribosomes Magnifications equal in all three cases 1 5 microns indicated

Glycogen is a normal constituent of the iris epithelial cells (Berkow & Fine 1970) A possible correlation between the vacuolisation and the increasing glycogen accumulation in diabetes should doubtless be considered

Translucency of the pigment epithelium is a characteristic clinical feature of diabetes As shown in Fig 1 a cell region displaying such a greatly reduced pigment content and at the same time accumulation of glycogen will possibly render the pigment epithelium translucent

The series under review allows of no conclusions as to whether the changes in the pigment granules observed are specific of diabetes It is surprising however that such changes were present in all the cases examined though in different degrees

The well known operative pigment liberation in diabetics which presumably is attributable to change of the pigment epithelium possibly bears relation to the above findings

References

Berkow J W & Fine B S (1970) Glycogen in normal human iris pigment epithelium *Amer J Ophthal 69* 994–996
Feeny L Grieshaber J A & Hogan M J (1965) *Studies on human ocular pigment* In Rohen J W ed (1965) *Eye Structure* II pp 535–548 Schattauer Verlag Stuttgart
Hollenberg M J & Burt W L (1969) The fine structure of Bruch s membrane in the human eye *Canad J Ophthal 4* 296–306
Hollenberg M S Nayyar R P & Burt W L (1968) *Histochemical* and electron microscopic studies of the retinal pigment epithelium in the normal and diabetic rat *Canad J Ophthal 3* 65–6
Hvidberg Hansen J (1971) unpublished data
Kamocki V (1887) Patologisch anatomische Untersuchungen von Augen diabeticher Individuen *Arch f Augenh 17* 24 –256
Thornell L E (1969) Personal communication
Yanoff M Fine B S & Berkow J W (1970) Diabetic lacy vacuolation of iris pigment epithelium. *Amer J Ophthal 69* 201–210

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INFLUENCE OF SOME AGENTS ON CORNEAL PERMEABILITY OF FLUORESCEIN IN VITRO

BY

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FOLLOW UP OF INITIALLY NONGLAUCOMATOUS PATIENTS WITH FIBRILLOPATHIA EPITHELIOCAPSULARIS (SO CALLED SENILE EXFOLIATION OF THE ANTERIOR LENS CAPSULE)

BY

MAGNUS ODLAND and HENRY AASVED

It is well known that patients with fibrillopathy (so called senile ex foliation) relatively often have open angle glaucoma The frequency appears to be about 25% (Aasved 1971) It is equally certain however that many of these patients do not suffer from glaucoma. It is never theless generally considered that patients with fibrillopathy should be examined at regular intervals due to the risk of subsequent development of glaucoma
There are however a few earlier studies which indicate that this risk may not be very great (Klouman 1967 Hansen & Sellevold 1970 Aasved 1971) This is a problem of practical clinical significance The present study presents a follow up of initially non glaucomatous patients with fibrillopathy registered at the Department of Ophthalmology University of Bergen since it opened in 1961

Key words fibrillopathia epitheliocapsularis – pseudoexfoliation – glau coma.

Material and Methods

The material embraces 67 patients 43 women and 24 men 32 having fibrillo pathy in both eyes Seven patients in whom borderline levels in the water

drinking test and tonography originally led to the diagnosis of suspected open angle glaucoma were also followed up

The intraocular pressure was measured with a Schiotz weight tonometer taking 4 0/5.5 as the upper normal limit. In about half the patients the intra ocular pressure was measured regularly at intervals of not more than 1 year whereas the others were examined less often as few as 2 registrations being made in some patients Registration of intraocular pressure was discontinued if there were modifications in the eye capable of influencing intraocular pres sure e g cataract surgery

The average intraocular pressure in the 99 eyes with fibrillopathy on initial registration was 15.2 mm Hg varying from 10.2 to 20 4 mm Hg The average intraocular pressure was the same in men and women, and as other factors were very similar the two sexes are presented together

Results

Table I shows the follow up time and the number of patients who developed open angle glaucoma or suspected open angle glaucoma. In all 3 of the 67 patients developed glaucoma during the follow up period One of these was among the 18 patients followed up for 2–3 years whereas in the two others glaucoma was discovered 8–9 years after the initial registration

In a fourth patient the intraocular pressure rose to borderline values in one eye after 4–5 years.

Fig 1 shows the age distribution of the 67 patients on initial registration of fibrillopathy and on the demonstration of glaucoma or suspected glaucoma. Most of the patients with fibrillopathy were in the age group 70 to 79 years The 3 patients in whom glaucoma developed were aged 67 83 and 92 years

Table I
Follow up time and development of glaucoma or suspected glaucoma in 67 patients with fibrillopathy

Years	2–3	4–5	6–7	8–9	Total
Number of patients	18	19	13	1	6
Development of glaucoma	1			2	3
Suspected glaucoma		1			1

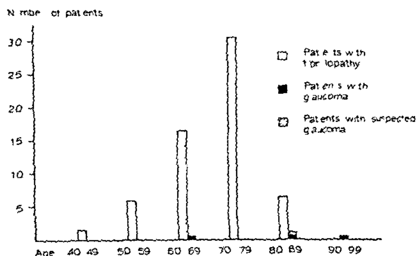


Fig 1

Age distribution of 6 patients when fibrillopathy was discovered in one eye and when glau oma or suspected glaucoma was registered

Table II

Intraocular pressure in the patients with fibrillopathy who developed glaucoma or suspected glaucoma

Patient no	Age	Eye	Initial pressure registration	Pressure when glaucoma discovered	Fibrillopathy	Follow up period
1	92	right eye left eye	13 4 13 4	12 2 43 4	bilateral	8 ¹/ years
2	83	right eye left eye	17 3 17 3	49 1 18 9	bilateral	8 ¾ years
3	67	right eye left eye	17 3 17 3	glaucoma discovered 17 3	unilateral (right eye)	3 years
4	80	right eye left eye	12 2 12 2	12 2 24 4 (suspected)	bilateral	4 years

respectively whereas the patient in whom borderline values developed was 80 years old

Table 2 shows the change in intraocular pressure in the 4 patients who developed pathlogical or borderline values Patient no 1 had not been re examined between the initial registration and a follow up 8 1/ years later Absolute glaucoma was demonstrated in the left eye but the pressure in the right eye was still normal Patient no 2 had normal pressure 5 years after the initial registration but pathological pressure in the right eye 3 years later In patient no 3 an eye specialist outside the hospital diagnosed capsular glaucoma in the right eye 3 years after the initial registration Patient no 4 was admitted to the Eye Department for cataract surgery 4 years after the initial registration and borderline pressure was then found in one eye

In the other 63 patients no change in the intraocular pressure of the 92 fibrillopathous eyes took place during the follow up period

A reexamination after 3–8 years of the 7 cases initially diagnosed as sus pected glaucoma showed open angle glaucoma in 2 cases the remaining 5 being again registered as borderline cases

Conclusion

The most important finding of this study is that most of the initially non glaucomatous patients with fibrillopathy did not develop glaucoma in the course of a follow up period of 2–9 years This accords well with earlier studies (Klouman 1967 Hansen & Sellevold 1970 Aasved 1971) These studies also in dicate that it was primarily in the first few years following the initial registra tion that the development of glaucoma took place This is in accordance with that found in the present study although the material is too small to demon strate any particular tendency In the one patient in whom glaucoma was de monstrated 8–9 years after the initial registration the glaucomatous eye was already amaurotic and the increase in intraocular pressure may thus have taken place many years earlier

The fact that the frequency of glaucoma in patients with fibrillopathy is nevertheless relatively high may indicate that the danger of the development of glaucoma is greatest at about the time fibrillopathy develops subsequently decreasing heavily This also accords with the finding that the frequency of glaucoma in patients with fibrillopathy shows no tendency to increase with increasing age as in the general population (Aasved 1971)

If a patient is found to have fibrillopathy but not glaucoma it is reasonable

to follow the patient for 2–3 years If the intraocular pressure remains normal the danger of the subsequent development of glaucoma will probably not be greater in patients with fibrillopathy than in other nonglaucomatous persons in the same age group

Summary

A follow up study covering 2–9 years of 67 initially nonglaucomatous pat ients with fibrillopathy (99 eyes) showed the development of open angle glaucoma in 3 persons (3 eyes) whereas the intraocular pressure had risen to borderline level in on person (1 eye) In the remaining 63 persons the intra ocular pressure had remained normal *in the fibrillopathous eyes* The danger of the development of glaucoma in persons with fibrillopathy appears to be greatest in the period during which fibrillopathy develops later decreasing heavily

References

Aasved H (1971) Intraocular pressure in eyes with and without fibrillopathia epitheliocapsularis *Acta opthal (Kbh) 49* 601–610

Hansen E & Sellevold O J (1969) Pseudoexfoliation of the lens capsule II Development of the exfoliation syndrome *Acta ophthal (Kbh) 47* 161–173

Hansen E & Sellevold O J (1970) Pseudoexfoliation of the lens capsule III Ocular tension in eyes with pseudoexfoliation *Acta ophthal (Kbh) 48* 446–454

Klouman, O S (1967) Pseudoexfoliation in ophthalmic practice *Acta ophthal 45* 822–873

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IMPORTANCE OF CALLOSAL TRANSFER IN THE EXTRAMACULAR INHIBITION PHENOMENON ALONG THE HEMIOPIC BORDER

BY

NIELS EHLERS

The hemiopic border may be demonstrated in normal subjects by 2 object campimetry as an inhibition of the perception of one of the objects When two horizontally disparate objects pass the border the perception of the first object is inhibited After a certain distance where only one object can be seen the first distinctly reappears After a further movement the second object also becomes distinct This phenomenon has been studied with various object sizes and distances In 7 patients with *agenesia corporis callosi* no inhibition could be demonstrated suggesting a callosal transfer in the normal inhibition
The inhibition phenomenon probably illustrates the adaptation mechanism which must exist in order to correlate the function of the two hemiretinae

Key words extramacular inhibition phenomenon – corpus callosum – hemiopic border – 2 object perimetry

The hemiopic border is the vertical line separating the areas of crossed and uncrossed optic fibres This line often called the visual vertical meridian also separates between the two cerebral hemispheres It becomes clinically manifest in the hemiopias but by a simple 2 object campimetry it may be visualized in normal subjects as an inhibition of the perception of one of the objects (Ehlers 1970) The present communication reports the absence of this inhibition phenomenon in 7 patients with *agenesia corporis callosi*

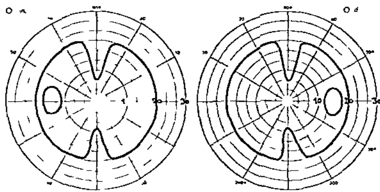


Fig 1

Visual fields for 2 object perception Outer limit for separation of two 6 mm white objects separated horizontally by 18 mm For explanation see text
Case FK man 33 years old

2-object campimetry

By campimetry with two neighbouring horizontally disparate objects the borders of the field of 2 object perception may be found as illustrated in Fig 1 Within a certain peripheral limit the two objects are perceived as two but along the vertical through the fixation point there are zones in the form of wedges pointing from above and from below towards the fixation point where only one object is seen In the central visuel field corresponding to the macular area (5–8 degrees from the fixation point) two objects are constantly seen.

Studies have been made as ordinary campimetry using a distance of 2000 mm for examination The size of the objects have been 6 10 20 and 36 mm The distance between the two objects have been varied between 18 and 120 mm The separation of the objects in the peripheral field of vision is difficult The position of the isoptres varies with training and attention for which reason statements of the size of fields will not be made Greater objects are more easily separated and within a certain limit the greater the distance between the two objects the more easily are they recognized as two 20 mm objects may generally be separated 30 degrees from the fixation point the usual outer limit in campimetry at 2000 mm. The two objects are more easily recognized when thew are separated angularly than when they are meridionally separated

More than a hundred subjects (members of the hospital staff and patients) have been examined and no significant individual variations have been ob

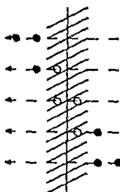


Fig 2
An illustration of the inhibition phenomenon along the hemiopic border as this is crossed by two horizontally disparate objects For explanation see text

served except for a few cases of tilting of the zones around the fixation point This is the reason why the designation hemiopic border is preferred to the visual vertical meridian

Analysis of the inhibition phenomenon

When the two objects pass the hemiopic border it is the first object that disappears After a certain distance when only one object can be perceived the first object distinctly reappears and after a further movement corresponding to the distance between the two objects the second also becomes distinct Fig 2 illustrates this sequence of events which may be elicited in passing from temporal to nasal as well as from nasal to temporal hemiretina

When the separation of the two objects was increased a distance was reached when no inhibition was observed This distance increased with the excentricity e g 15 degrees from the fixation point it was around 90 mm If the two objects are vertically separated when they pass the hemiopic border no inhibition can be observed A small vertical separation in addition to the horizontal separation does not prevent the inhibition With greater vertical separation the observation is very difficult probably no inhibition exists

Agnesia corporis callosi

Seven patients with this disorder were studied In 4 cases the diagnosis was verified by operation in the remaining 3 it was made by pneumoencephalo-

graphy (see e g Unterharnscheidt et al 1968) All patients cooperated well in the examination

None of these 7 patients could recognize the inhibition phenomenon At first the examination was made without it having been explained The patients constantly perceived two objects when these passed the hemiopic border Then it was explained that most people can see only one object when the two objects passed the hemiopic border All patients maintained that they could see two objects

Discussion

In the earlier ophthalmological literature functional differences between the nasal and the temporal hemiretina was reported (*Brændstrup 1948a b*)

During recent years the relation between the nasal and the temporal hemi retina has again received a growing interest It has been demonstrated in cats and monkeys that the area along the hemiopic border is represented in the cerebral cortex at the 17/18 boundary This cerebral area is connected to the same area in the opposite hemisphere through the corpus callosum (Myers 1962 Berlucchi et al 1967 1968 Chowdhury et al 1965 Hubel & Wiesel 1967) In the cat retina a zone along the hemiopic border was found to have projections to both hemispheres (Stone 1966 Leicester 1968)

The inhibition along the hemiopic border is a normal phenomenon The present observation suggests that it is related to an interhemispheric commissure through the corpus callosum However it must be admitted that the negative statement of the 7 patients viz that they could not experience any inhibition along the hemiopic border cannot be considered a definitive proof

The clinical demonstration of the inhibition is probably only an illustration of the adapting mechanism which links together the two half visual fields If the normal inhibition prevented diplopia along the hemiopic border it could be expected that in patients with *agenesia corporis callosi* double vision could be demonstrated All 7 patients were questioned about this which they all denied

Possible functions of an adapting mechanism located along the hemiopic border must be related to the perception of moved objects crossing the border but probably also to binocular visual perception which requires an accurate coordination not only of the two hemiretinae but also of the two eyes and the two cerebral hemispheres

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SIGNIFICANSE OF SUBRETINAL ABSORPTION FOR EFFECTIVENESS OF BUCKLING OPERATIONS

BY

BENGT ROSENGREN

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From the Eye Department
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EXPERIENCES IN SURGICAL TREATMENT OF HAEMORRHAGIC GLAUCOMA
A Follow up Study

BY

P H MADSEN

Treatment of the fully developed haemorrhagic glaucoma is difficult Surveys of the most commonly used methods of treatment have recently been published by Kruger (1963) Muller Jensen (1965) and Ohrt (1967) Miotics adrenaline and Diamox are usually ineffective Retrobulbar injection of alcohol results in satisfactory but often transient relief of pain The common filtering operations should scarcely be used because of the great risk of haemorrhage from the many large vessels on the iris and in the chamber angle
The best operations seem to be cyclodiathermy cyclocryothermy or filtering operation with electrocoagulation of iris and sclera by the methods of Preziosi (1924) or Ellis Thompson & Tyner (1962)
In the present paper the long term results after filtering operation with electrocoagulation are presented

Key words glaucoma – surgery

Material and Results

56 Patients with haemorrhagic glaucoma from the eye departments in Århus and Odense were treated in the years 1963–1970 Data concerning the patients appear from Table I Nearly all patients were operated on account of intense pain which otherwise would have necessitated an enucleation of the eye 25 of the patients had diabetes mellitus in most of the cases with proliferative

Table I
General data of 56 patients with haemorrhagic glaucoma

	Århus	Odense
No of patients	30	26
Diabetes mellitus	13	12
Men/women	17/13	9 17
Average age	62	60
Operation performed	Preziosi	Modified Scheie
No of eyes	32	30

retinopathy Central venous thrombosis was observed in the majority of the non diabetics A difference in the sex distribution was noted among the patients from the two clinics otherwise the two groups were comparable

In Århus 32 eyes were operated by the method of Preziosi (Preziosi 1924 Merte 1963) After preparation of a conjunctival flap electrocautery was used to make the fistulous track at the site of the filtration angle If the iris prolapsed or adhered to the cornea it was punctured with the electrocautery but no iridectomy was performed

In Odense 30 eyes were operated by another technique Entrance to the chamber angle was achieved by alternating incision and electrocoagulation (Scheie 1959) and in performing the iridectomy diathermy was also employed (Ellis Thompson and Tyner 1962 Wille Jorgensen 1966)

The operations were performed with utmost caution to avoid haemorrhage from the new formed rubeosis vessels on the iris and in the chamber angle

The immediate effect was nearly always complete relief of pain and the intraocular pressure became normal or subnormal An analysis of the operative results at discharge would thus suggest a good effect of both operations How ever in order to get an impression of the long term results check up exami nations were performed The results appear from Table II In the case of repeated examinations the last observation was recorded in the table The assessment is thus based on observations made over periods ranging from a few months to six years after the operation

Visual acuity above 6/60 was only preserved in three eyes Thus in the table only the absence or presence of pain and the level of the intraocular pressure are recorded. As it appears among 41 eyes observed for 6 months or more 36 (88 per cent) remained painless and the intraocular pressure was normal in 22 (54 per cent) The table also includes patients with short observation time

Table II
Long term results of operation for haemorrhagic glaucoma.

Time of observation	No of eyes	Pain		Normal intraocular pressure
		Present	Absent	
Preziosi				
> 12 months	18	3	15	8
6–12 months	3	1	2	1
< 6 months	11	3		
Scheie				
> 12 months	17	1	16	11
6–12 months	3	0	3	2
< 6 months	10	2		

as well as patients who died or – for some other reason – did not return for check up examination. In five out of 21 eyes severe pain recurred within the first six months after the operation.

In the whole material eight eyes had to be removed (13 per cent) 5 eyes after Preziosi s operation, 3 after the modified Scheie operation

Conclusion

Haemorrhagic glaucoma is a serious disease. In nearly all cases vision is lost and the only objective of the treatment is to relieve the pain, which is often very intense. In melanoma of the choroid, a secondary glaucoma may assume a haemorrhagic character with new vessels on the anterior iris surface and in the chamber angle (Skydsgaard 1948 Brændstrup 1950 Madsen 1971)

In the abscence of a tumor a filtering operation with electrocoagulation of the iris should be preferred to enucleation of the eye. From this series it appears that 36 out of 41 eyes remained painless for 6 months or more after the operation.

Preziosi s operation and Scheie s operation with electrocoagulation of the iris according to the method of Ellis Thompson & Tyner (1962) are well suited for haemorrhagic glaucoma no difference was found in the effect of the two interventions

References

Brændstrup P (1950) Central vein thrombosis and haemorrhagic glaucoma *Acta ophthal (Kbh) Suppl 35*
Ellis P P Thompson R L & Tyner G S (1962) *Amer J Ophthal 54* 954–960
Kruger S (1963) *Fortschr Augenheilk 14* 1–50
Madsen P H (1971) *Brit J Ophthal 55* 444–450
Merte H J (1963) *Klin Mbl Augenheilk 142* 548–554
Muller Jensen K (1965) *Klin Mbl Augenheilk 146* 718–722
Ohrt V (1967) *Diabetic iridopathy* Universitetsforlaget i Aarhus
Preziosi C. L (1924) *Brit J Ophthal 8* 414–417
Scheie H G (1959) *Arch Ophthal 61* 291–297
Skydsgaard H (1948) *Acta ophthal (Kbh) 26* 135–151
Wille Jørgensen, A (1966) *Acta ophthal (Kbh) 44* 261–263

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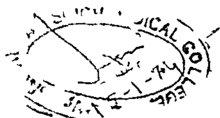
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THE SUPRASELLAR MENINGIOMA

A Review of the Literature and Presentation of a Series of 31 Cases

Niels Ehlers Richard Malmros



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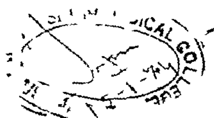
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1973

THE SUPRASELLAR MENINGIOMA

ACTA OPHTHALMOLOGICA
SUPPLEMENTUM 2

THE SUPRASELLAR MENINGIOMA

A Review of the Literature and Presentation of a Series of 31 Cases

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TABLE OF CONTENTS

INTRODUCTION

MATERIAL

Previous series	10
Present series	14
Age	14
Sex	17
Asymptomatic suprasellar meningioma	18

CLINICAL FEATURES

Subjective symptoms	19
Failing vision	19
Temporal constriction of the visual fields	19
Periocular pain	20
Diplopia	20
Visual hallucinations	20
Visual acuity	21
Visual fields	22
Ophthalmoscopy	25
Other neurological findings	26
Headache	26
Symptoms from the hypophysis and the hypothalamus	26
Anosmia	26
Mental changes	26
Spinal protein	27
Electro-encephalography	27
Influence of pregnancy	27
Analysis of pre-operative clinical findings – positive diagnosis	27
Duration of symptoms	27
Case histories (Nos 25 12 3 4 14 17 and 18)	29
Age distribution	36
Sex	36
Tumour size	36
Histopathology	37
Exact localization of the suprasellar meningioma	37

INTRODUCTION

A suprasellar meningioma is here in accordance with Cushing & Eisenhardt (1938) and Olivecrona (1967) defined as a tumour arising from the pre sellar area around the tuberculum sellae and growing upwards between the two optic nerves In the literature these tumours are often called meningiomata of the tuberculum sellae although this anatomical structure need not be their site of origin

Cushing described four stages of this tumour His diagrammatic illustration (Fig 1) is reproduced here as it gives a good impression of the anatomical relations which explain the almost exclusively ophthalmological signs and symptoms of the tumour Stage I is the initial and II probably still presymptomatic Stage III is symptomatic and surgically favourable while stage IV corresponding to a tumour weight of about 20 g is surgically unfavourable The tumour originates from arachnoidal cells in the dura and in the villous processes of the venous sinuses (Russell & Rubinstein 1971)

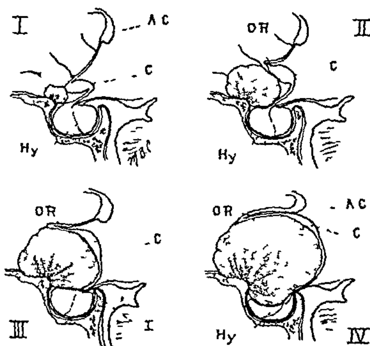


Fig 1 Cushing's illustration of the four stages of a suprasellar meningioma I is the initial stage II probably still presymptomatic III is symptomatic and surgically favourable while stage IV corresponding to a tumour weight of about 20 g is surgically unfavourable Courtesy of Charles C Thomas Publisher Springfield Illinois

DIFFERENTIAL DIAGNOSIS
Problems in the early diagnosis 38
Failing vision no optic atrophy 38
Failing vision and optic atrophy 38
Visual field defects 39
Causes of the chiasmal syndrome 39
Intrasellar tumours 39
Extrasellar tumours 39
Other lesions 43

RADIOLOGICAL FINDINGS
Radiography of the skull 4[illegible]
Angiography 47
Pneumography 49
Isotope scanning 50

TREATMENT
Indications for operation 52
Technique of operation 53

COMPLICATIONS OF OPERATION
Postoperative deaths (cases 8 and 10) 56
Pituitary hypothalamic insufficiency (case 21) 57
Other complications 59

RESULTS
Immediate visual results 60
Late results 60
Survival 6[illegible]
Recurrence 62

CONCLUSIONS AND SUMMARY

REFERENCES

mata of the anterior and medial cranial fossa treated in the Department of Neu rosurgery Århus Kommunehospital during the period from April 1 1943 to March 31 1971 were reviewed Table I is a survey of this series comprising 119 cases It is immediately evident that meningiomata grouped as suprasellar produce the re quired symptomatology The 50 cases of sphenoidal meningioma are characterized by temporal symptoms and papilloedema (globular tumours) or unilateral exoph thalmos and pareses of the extra-ocular muscles (en plaque meningiomata) The localization medial or lateral is obviously of the utmost importance in the symp tomatology The ethmoidal meningioma may produce ophthalmological symptoms similar to those of the suprasellar meningioma but this does not occur until the tumour is very large and gives rise also to other manifestations (anosmia frontal symptoms) The group of tumours from the medial cranial fossa appear rather heterogeneous but in this as well as in the two preceding groups cases showing transitions to suprasellar meningioma occur These will be considered in the section on the differential diagnosis

It is the purpose of this paper to give an account of the clinical picture diagnosi treatment and prognosis of the suprasellar meningioma This will be based on the 31 cases (Table I) subjected to operation in the Department of Neurosurgery Århus Kommunehospital *and on a survey of the literature*

MATERIAL

Previous series

In the literature extensively reported cases of suprasellar meningioma were found as summarized in Table V, comprising a total of 211 cases These case reports contain a wealth of information but many of them are selected in order to illustrate special aspects of the suprasellar meningioma Therefore they do not constitute a representative material Their greatest importance is that they illustrate the various clinical pictures which a suprasellar meningioma may produce

A large number of cases are also found in series mainly reported from neurosurgical or radiological units These cases are mentioned in a more cursory or tabular form The group comprises in addition to the series of Holmes & Sargent Cushing & Eisenhardt Guillaumat and Verin included in Table V the reports of Dechaume et al (1949) DiChiro & Lindgren (1952) Uihlein & Weyand (1953), Grant & Hedges (1956) Holub (1956) Cassinari & Bernasconi (1957) Newell & Beaman (1958) Tucker et al (1959) Jane & McKissock (1962), Passerini & Cecchini (1962) Weber (1965) Lombardi (1967) and Ley (1970) These series will be used mainly for comparison with the present series

A problem encountered in the use of the information found in the literature is the various definitions of a suprasellar meningioma Some authors consider the meningioma arising from the tuberculum sellae to be a special form of suprasellar meningioma and under the latter designation include any meningioma situated above the sella (Argañaraz 1931 Velter 1936 Guillaumat 1937 Philippides et al 1953 Birge 1955 Samii et al 1968) It is evident from a review of the literature that many of the tumours reported as suprasellar (or tuberculum sellae) meningiomata have been extremely large We believe that some of these should rather be classified as ethmoidal meningiomata Their treatment and course differ much from what applies to a typical suprasellar meningioma Cushing regarded tumours weighing more than 20 g as inoperable In this connection the 52 cases of meningioma of the anterior clinoid process reported by Uihlein & Weyand (1953) may present a problem From the high incidence of papilloedema and unilateral exophthalmos it must be assumed that these cases represent transitional forms mainly to sphenoidal meningiomata

A meningioma arising in the orbit has a clinical picture dominated by exophthalmos and affected movements of the eye and will hardly ever be mistaken for a suprasellar tumour while a meningioma in the optic canal may give rise to loss of vision and primary optic atrophy and thus be mistaken for a suprasellar mening

TABLE II

31 cases of suprasellar meningioma

Case record No	Serial No	Age (years)	Sex		Duration of history (years)	Age at onset of symptoms (years)	Size of tumour		Histological classification	
1830	1	61	F		17	44	L			F
2123	2	45	F		6	39	L			F
3030	3	49	F		10	39		S	E	
4415	4	52	F		4	48	L		E	
6624	5	39	F		0 3	39		S		F
7723	6	31	F		1	30		S	E	
8407	7	58	F		1	57	L		E	
9948	8	43	F		3	40	L		E	
10907	9	57		M	0 5	56		S		F
12266	10	37	F		3	34	L		E	
15686	11	51		M	7	44	L		E + F	
16898	12	60	F		0 1	60		S	E + F	
18630	13	37	F		2	35		S		F
18919	14	39	F		1	38		S		F
20508	15	43	F		0 5	43	L		E + F	
21095	16	45	F		0 3	45	L		E	
21489	17	39	F		0 6	38		S	E	
21489	18	47	F		2	45		S	E	
21877	19	59		M	1	58	L		E	
24413	20	52		M	0			S	E	
29075	21	72	F		3	69	L		E	
34084	22	63		M	1	62	L		E + F	
34741	23	41		M	0 3	41	L		E + F	
35186	24	55	F		0 3	55		S	E + F	
36500	25	34	F		1	33		S	E	
36876	26	62	F		0 5	62	L		E + F	
37378	27	56	F		5	51	L		E + F	
37788	28	55		M	0 3	55	L		E + F	
39277	29	37	F		1 5	35	L		E	
39365	30	72	F		4	68		S	E + F	
39380	31	39	F		1 3	38	L		E + F	

Data for 31 cases of suprasellar meningiomata operated on in the neurosurgical department G Århus Kommunehospital in the period 1 4 1943 to 31 3 1971

The size of the tumour is given as small or large In accordance with McKissock a small tumour has a diameter below 3 cm corresponding to a weight of approx 5 6 g The weight of the large tumours was in the range 10 to 25 g with a single exception (case 4) of an enormous tumour of 40 g

The histological classification is made according to Russell & Rubinstein (1971) E meaning endotheliomatous F fibrillar and E + F a mixed transitional form

TABLE III

OPHTHALMOLOGICAL EXAMINATION OF 31 CASES OF SUPRASELLAR MENINGIOMA

Case no	Preoperative examination						Po.,toperative examination						Follow-up examination							Comments
	VA L	VA R	Ophthal L	Ophthal R	Field L	Field R	VA L	VA R	Ophthal L	Ophthal R	Field L	Field R	Years of follow-up	VA L	VA R	Ophthal L	Ophthal R	Field L	Field R	
1	+L	0 05	A	A			-L	-L	A	A			no reexam	remained blind						dies after 13 y
2	FC	1 00	A	N			0 15	0 67	A	N			no reexam	useful vision to death						dies after 23 y
3	0 1	0 5	A	A			-L	-L	A	A			-							dies 21 d postop
4	1 00	-L	N	A			1 00	-L	N	A			24	0 5	-L	(A)	A			still alive
5	0 5	0 25	A	N			1 00	0 33	A	N			22	0 67	0 33	A	N			recurrence
6	0 67	-L	N	A			0 67	-L	N	A			no reexam							dies after 1 y
7	0 1	1 00	A	A			-L	0 25	A	A			4	-L	0 25	A	A			dies after 17 y
8	0 5	0 1	A	A									pituitary	insufficiensy						dies 5 d postop
9	0 67	+L	A	A			0 5	0 5	(A)	(A)			19	0 5	0 5	(A)	(A)			still alive
10	-L	0 33	A	N			-L	1 00	A	N			-							dies 18 d postop
11	0 67	FC	A	A			1 00	-L	A	A			no reexam	useful vision to death						dies after 14 y
12	0 33	0 5	N	N			1 00	1 00	N	N			16	-L	0 67	A	(A)			recurrence
13	0 33	1 00	N	N			1 00	1 00	N	N			5	1 00	1 00	N	N			die., after 15 y
14	FC	1 00	A	N			FC	1 00	A	N			15	FC	1 00	A	N			-
15	FC	FC	A	N			HM	0 33	A	A			14	-L	0 67	A	A			-

16	0 67	0 67	A	A			0 5	FC	A	A			13 5	0 67	-L	A	A			-
17	0 1	1 00	A	N			0 1	1 00	A	N			1 5	0 1	1 0	A	(A)			new tumour
18	-L	0 4	A	(A)			-L	0 67	A	(A)			6	-L	1 0	A	(A)			-
19	0 5	1 00	N	N			0 67	1 00	N	N			13	1 0	1 0	N	N			-
20	1 00	1 00	N	N			0 67	1 00	N	N			1	0 67	1 00	N	N			dies after 1 y
21	0 33	0 1	A	A			FC	0 33	A	A			1	0 1	0 33	A	A			dies after 8 y
22	FC	0 33	A	A			0 15	0 05	A	A			5	0 2	HM	A	A			-
23	1 00	L	N	A			1 00	L	N	A			4 5	1 0	L	N	A			-
24	0 33	0 67	N	N			1 00	1 00	N	N			4 5	1 0	1 0	N	N			-
25	0 4	HM	N	A			0 67	HM	N	A			3	1 0	HM	N	A			-
26	FC	0 5	A	A			0 4	1 00	A	A			3	1 0	1 0	(A)	(A)			-
27	-L	+L	A	A			-L	0 05	A	A			2 5	-L	0 67	A	A			-
28	0 67	0 5	N	N			1 00	0 67	N	N			2 5	1 00	0 67	N	A			
29	L	1 00	A	N			-L	1 00	A	N			1 5	L	1 0	A	N			
30	+L	0 9	A	N			0 25	1 00	A	N			1 0	1 00	1 00	N	N			
31	FC	1 00	A	N			FC	1 00	A	N			2	FC	1 00	A	(A)			-

The table shows the pre and postoperative ophthalmological findings as well as the result of the latest follow up examination I = light perception HM = handmovements FC = finger counting N = normal disc A = atrophic disc (A) = slightly atrophic disc * after case No indicates that the full case history is given

ioma This was the case in the only patient we have seen A rare combined supra sellar and optic nerve meningioma was reported by Cairns (1938) Optic nerve meningiomata may arise also from the intracranial part of the nerve To the latter group belong the cases operated on by Dandy (1922) Orbital and optic nerve meningiomata will not be considered in this paper

Present series

During the period from April 1, 1943 to March 31, 1971 a total of 31 cases of suprasellar meningioma were subjected to operation in the Department of Neu rosurgery Arhus Kommunehospital (Table I) In the same period a total of 2383 intracranial tumours were verified at operation Of these 2383 tumours, 354 (14 8 %) were meningiomata This frequency is in accordance with the figures in the literature (Cushing & Eisenhardt 1938, 13 4 %, Olivecrona 1967, 18 4 %) In our series 31 of the 354 meningiomata (8 8 %) were suprasellar This frequency is also within the range reported in the literature (Cushing & Eisenhardt 9 5 %, Guillaumat 1937, 9 9 % Guillaume et al 1957 6 2 % Olivercrona 7 1 % Tables II and III present data for the 31 cases of our series

Our ophthalmological examinations comprised determination of visual acuity at 6 m ophthalmoscopy and perimetry on a 2 m Bjerrum screen, an arc perimeter or the Goldmann perimeter Effective visual acuity based on current Scandinavian tab les for assessing visual disability due to reduced central vision (Vesterdal 1969) was used for comparison Likewise an evaluation of the visual fields was made using the functional grid score , as described by Esterman (1967 1968) This is a simple means of obtaining a single figure characterizing the percentage of retained visual field The average of the two eyes was used to characterize the case

Age

Cushing & Eisenhardt (1929) stated that suprasellar meningioma should be expect ed in middle aged persons The actual age distribution of 213 patients with me ningioma at the onset of symptoms is shown in Fig 2 The lesion is seen to occur throughout adult life from 16 to 69 years of age most frequently between 35 and 45 The average age of the patients is 40 7 years The youngest cases have been reported by Schlezinger et al (1946) Philippides et al (1953) and Weyand et al (1951) Suprasellar meningioma has also been reported to occur in childhood (for references see Verin 1963) Apparently, the youngest patient was a 21 month old boy described by Ruggiero (1957) It may be added that one of the cases of Uihlein & Weyand (1953) with a meningioma from the anterior clinoid process had been blind since the age of 6 years The oldest patients are found in the present series (two women aged 69 Nos 21 and 30) and in the report of Forster & Bouzarth (1967)

The present series suggests a difference in age distribution between women and men (Fig 3) The average age of the women was 45 3 years of the men 52 7 years at the onset of symptoms The corresponding ages on admission were 48 0 years for women and 54 0 years for men In a series of 313 meningiomata Cushing & Eisen hardt (1938) noted the same tendency the average age on admission was 46 6 years but the average for women (43 years) was nearly 10 years less than that for men (52 years) An analysis of the cases shown in Fig 2 reveals an age distribution of the women similar to that of the entire group, while the male cases are more evenly distributed over the entire range

TABLE IV

Effective central vision and visual field score

Case	Effective central vision			Visual field score		
	pre operative %	post operative %	follow up %	pre operative %	post operative %	follow up %
1	0	0	–	20	0	–
2	85	90	–	57	88	–
3	85	0	–	40	0	–
4	80	80	80	23	20	20
5	90	95	90	59	100	67
6	80	80	–	50	50	–
7	88	40	–	70	50	–
8	85	–	–	40	–	–
9	80	95	95	25	57	90
10	55	80	–	21	70	–
11	85	80	–	33	49	–
12	90	100	80	100	100	70
13	95	100	100	100	100	100
14	85	85	84	64	64	69
15	5	60	80	40	28	24
16	100	80	80	40	25	15
17	88	88	88	40	67	67
18	55	80	80	–	30	34
19	100	100	100	79	97	100
20	100	100	100	100	100	100
21	65	60	65	40	40	40
22	60	30	25	21	61	9
23	80	80	80	43	50	50
24	95	100	100	31	100	100
25	80	80	80	13	56	52
26	80	100	100	30	100	100
27	0	30	80	7	16	20
28	100	100	100	90	90	90
29	80	80	80	50	50	50
30	85	85	100	44	57	100
31	80	92	88	27	50	50
Mean	76	77	85	47	57	62

*The table shows effective vision in percent Visual acuity is evaluated from the current Scan*dinavian table for assessing disability due to reduced central vision (Vesterdal 1969)
Evaluation of the visual field is made by the „functional grid score as reported by Esterman (1967 1968) The score is given as the average for the two eyes

TABLE V

Cases of suprasellar meningioma reported in the literature

Authors	Year	No of cases	Women	Men
Holmes & Sargent	1927	10	6	4
Olivecrona	1927	1	1	–
van Bogaert	1929	1	–	1
Cushing & Eisenhardt	1929/38	28	21	7
Guttmann & Spatz	1929	3	2	1
Davis	1931	1	1	–
Fischer	1931	1	1	–
Learmonth et al	1931	1	1	–
Marx & Boeve	1932	1	1	–
Globus	1933	1	1	–
Alajouanine et al	1934	1	1	–
Bucy & Kredel	1934	1	–	1
Manolesco & Schmitzer	1934	1	1	–
Towne	1934	1	–	1
Velter	1936	2	1	1
Dollfus et al	1937	1	–	1
Guillaumat	*1937*	22	*17*	5
Hagedorn	1937	1	1	–
Williamson Noble	1939	1	1	–
Anker	1941	1	–	1
Espinosa	1946	2	1	1
Mathewson	1946	1	1	–
Schlezinger et al	1946	4	4	–
Meadows	1949	4	2	2
Chambers	1950	1	–	1
Coulonjou et al	1950	1	1	–
Alport	1951	1	1	–
Weyand et al	1951	6	6	–
Bardram & Moller	1952	5	3	2
Joy	1952	1	1	–
Philippides et al	1953	3	3	–
Bocci	1954	1	1	–
Busch & Mahneke	1954	1	1	–
Davidoff & Epstein	1955	2	–	2
Glees & Zielinski	1956	1	1	–
Newell & Beaman	1958	2	1	1
Walsh & Gass	1960	1	1	–
Rucker & Kearns	1961	5	3	2
Udvarhelyi & Walsh	1962	2	2	–
Vérin	1963	83	66	17
Enoksson	1965	1	1	–
Forster & Bouzarth	1967	1	1	–
Hugonnier et al	1968	2	2	–
Total No		211	160	51

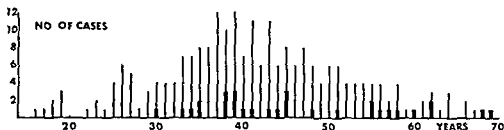


Fig 2 The distribution of the age at onset of symptoms of 213 patients with suprasellar meningioma Data collected from the literature Thick olumns represent the cases of the present series

Fig 3 The distribution of the age at onset of symptoms (left) and at operation (right) of the patients from the present series

Sex

It is well recognized that meningiomata are more frequent in women than in men the ratio being 3 to 2 (Cushing & Eisenhardt 1938 Horrax 1939) This female preponderance seems even more pronounced in suprasellar meningiomata The 31 patients in our series were 24 women and 7 men and among the cases considered in Table V there were 51 men and 160 women This difference is statistically significant (binomial distribution, $P < 0.01$) It may be concluded that suprasellar meningiomata occur with a M/F ratio of about 1 to 3 This is supported by many additional figures from the literature, e g Holub (1956) 6M/18F, Tucker et al

(1959) 12M/39F Jane & McKissock (1962) 14M/39F, Passerini & Cecchini (1962) 3M/21F, Weber (1965) 13M/32F and Lombardi (1967) 6M/28F

It may be added that pituitary adenomata occur with an equal frequency in men and women (Elkington & McKissock 1967) while intracranial aneurysms show some female preponderance (Hamby 1952) Craniopharyngiomata also occur with an equal frequency in the two sexes

Asymptomatic suprasellar meningioma

A suprasellar meningioma found post mortem or unexpectedly at operation was reported by Heinrichsdorff (1914) Cushing & Eisenhardt (1929), Guttmann & Spatz (1929) Towne (1934), and was seen in two patients of the present series The first patient (No 13) was a 37 year old woman operated on for a saccular aneurysm of the left internal carotid artery The aneurysm gave rise to acute development of left oculomotor paresis, dim vision had been present in the left eye (0 33) for two years A meningioma the size of a hazelnut, was removed from the tuberculum sellae The second patient (No 20) was a 52 year-old man who was operated on for a sphenoidal ridge meningioma A small tuberculum sellae meningioma (4 g) which was asymptomatic both before and after the operation, was removed A very interesting case was reported by Hardy & Robert (1969) In an autopsy study they found a sub diaphragmatic intrasellar meningioma 3 mm in diameter Guillaumat (1937 case 5) Passerini & Cecchini (1962) and Cophignon et al (1969) reported cases of suprasellar and intrasellar meningiomata

CLINICAL FEATURES

Subjective symptoms

The most common initial subjective symptom is a complaint of *failing vision* by the patient described in more or less detail as a mist or shadow before the eye but sometimes only as dim vision The description of the onset of the visual disturbance is commonly vague without the positive scotoma of retrobulbar neuritis Sometimes the accidental closing of one eye has revealed that the other had little or no vision In the present series failing vision was reported as the single subjective complaint in 21 cases This is in good agreement with the observations of Cushing & Eisenhardt (1938) Guillaumat (1937) and Verin (1963) It may be concluded that about 75 % of suprasellar meningiomata present with monosymptomatic failing vision in several cases in one eye only Far less frequently the patient has been aware of a *temporal constriction of the visual field* in one or both eyes Statements in the literature about this do not seem reliable and might easily have been induced

TABLE VI

Subjective symptoms in suprasellar meningiomata

Symptoms	Cushing & Eisenhardt 1929 1938	Guillaumat 1937	Olivecrona Verin 1963	Present series 1973
Failing vision	25	18	47	22
Temporal field constriction	2	2	25	7
Diplopia	1	–	6	3
Headache	6	12	36	8
Hypophyso-hypothalamic symptoms	1	–	15	–
No subjective symptoms	1	1	–	2
Pressure symptoms	1	2	–	–
No information	1	1	–	–
No of cases	28	22	83	31

The table is based on an analysis of the materials published by Cushing & Eisenhardt (1929 1938) Guillaumat (1937) and Verin (1963) as well as the present series

(1959) 12M/39F, Jane & McKissock (1962) 14M/39F, Passerini & Cecchini (1962) 3M/21F, Weber (1965) 13M/32F and Lombardi (1967) 6M/28F

It may be added that pituitary adenomata occur with an equal frequency in men and women (Elkington & McKissock 1967), while intracranial aneurysms show some female preponderance (Hamby 1952) Craniopharyngiomata also occur with an equal frequency in the two sexes

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the eyes for the last 12 months and a positive scotoma in the left eye for the last few days before admission This eye showed a visual acuity of 0 67 and normal perimetry and ophthalmoscopy In the second case a 45 year-old woman had experienced slowly progressive intermittent light flashes before the eyes occurring simultaneous with decreasing vision Examination showed slightly reduced visual acuity (0 67) bitemporal hemianopia and pale discs It may be difficult to interpret these few reports Some affection of the vitreous which was not ruled out in any of the cases seems probable On the other hand it cannot be definitely excluded that an irritative phase may in some cases precede the functional deterioration

Visual acuity

In agreement with the fact that a complaint of failing vision is a frequent symptom reduced visual acuity is nearly always present This may be of any degree ranging from the slightest to no light perception Table VII summarizes the pre-operative visual acuity findings from the literature and from the present series Very commonly one eye is severely affected while the other shows normal or only slightly reduced visual acuity (Grant & Hedges 1956) Eighteen of our 31 patients had visual

TABLE VII

Pre operative visual acuity in suprasellar meningioma

Visual acuity	Cushing & Eisenhardt 1938	Gullhumar 1937	Olivecrona Vénn 1963	Present series 1973 pre op	Present series post op
Normal in both eyes	0	0	0	2	3
Normal in first eye slightly reduced in second eye	0	0	2	1	4
Normal in first eye medium reduced in second eye	0	0	11	3	3
Normal in first eye severely reduced in second eye	0	4	14	6	7
Slightly reduced in both eyes	1	0	4	1	1
Slightly reduced in first eye medium reduced in second eye	3	2	4	5	1
Slightly reduced in first eye severely reduced in second eye	5	2	13	7	4
Medium reduced in both eyes	2	1	3	1	0
Medium reduced in first eye severely reduced in second eye	8	3	18	2	4
Severely reduced in both eyes	5	7	13	3	3
Total No	24	19	82	31	30

Slightly reduced = visual acuity > 0.33
Medium reduced ~ 0 33 ≥ visual acuity ≥ 0 1
Severely reduced = visual acuity < 0 1

acuity in one or both eyes reduced to finger counting or less at the pre operative examination (Table III) In five cases, one eye had ± light perception, whereas the other eye had normal visual acuity Among 14 patients Newell & Beaman (1958) found that at the first examination 11 had visual acuity in one eye of less than counting fingers before the eye Fortunately, bilateral severely reduced visual acuity is found mainly in the older literature but it may still be encountered (Table III, case 27)

Visual fields

Bitemporal defects are important and typical, the other frequent finding being one blind eye and various temporal defects in the other Table VIII summarizes the pre operative visual field findings in the present and other series Regular bitemporal hemianopias are found, but frequently the defects are characterized by asymmetry (Fig 4) Horizontal hemianopias and scotomatous defects may also be observed (Glees 1956 Glees & Zielinski 1956) (Fig 5) Arcuate scotomata known from

TABLE VIII

Pre operative visual field findings in suprasellar meningioma

Field defects	Cushing & Eisenhardt 1929 1938	Guillaumat 1937	Weber 1965	Present series 1973
Bitemporal hemianopia	10	3	8	7
Bitemporal quadrant defects	1 (upper)	2 (lower)	–	1 (upper)
Bitemporal scotomata	–	–	1	1
Other bitemporal defects*)	2	3	4	5
Homonymous defects	1	–	2	–
First eye blind**)				
Second eye blind	1	1	1	–
Second eye normal	–	–	7	2
Second eye temp hemianopia	7	3	12	2
Second eye other temp defects	2	5	–	3
First eye normal				
Second eye normal	–	–	1	2
Second eye temp hemianopia	–	1	8	1
Second eye other temp defects	–	1	–	4
Altitudinal defects				
Bilateral lower hemianopia	–	–	–	1
Irregular defects	1 (scotoma)	1	1	2
No information	3	2	–	–
Total	28	22	45	31

*) This group includes various more or less irregular defects all of definite bitemporal nature The group is variously specified by different authors Detailed information about the present series is found in Table III

** Blind refers to visual acuity ± light perception field examination not possible

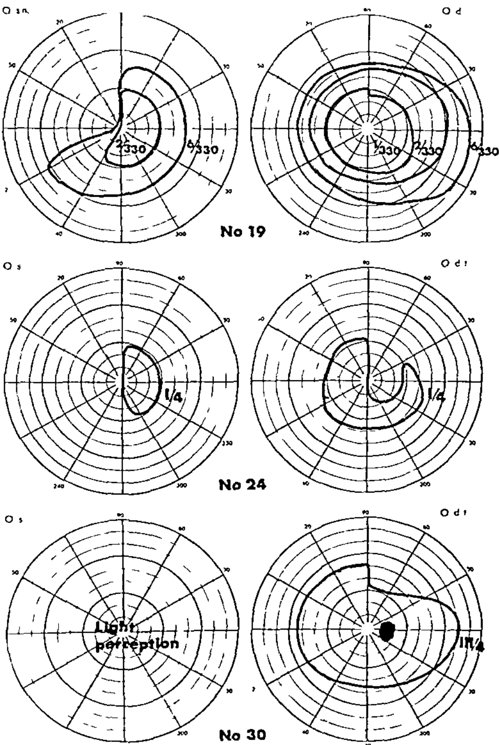


Fig 4 Asymmetrical bitemporal visual field defects Pre-operative findings in patients with suprasellar meningioma Cases 19 24 and 30

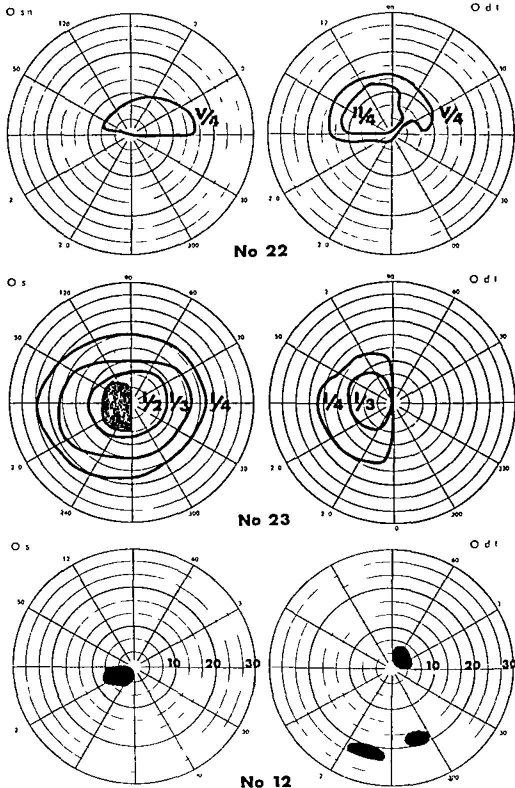


Fig 5 Horizontal and scotomatous visual field defects Pre operative findings in patients with suprasellar meningioma Cases 22 23 and 12

pituitary adenomata (Smith 1965) have not been described in suprasellar meningioma Homonymous defects on the other hand are reported in the literature but did not occur in our own series

A specific type of field defects or a characteristic development as known from pituitary adenoma does not seem to exist in suprasellar meningioma (Brouwer 1929 Weber 1965 and others) although central or paracentral scotomata are reported to be early signs (Schlezinger et al 1946 Kelly 1963) In analysing the visual fields in suprasellar meningiomata it should be realized that lesions may be localized not only in the chiasma but also in the optic nerves A pre or post fixed chiasma (de Schweinits 1923 Schaeffer 1924) individual variations in angio-architecture (François et al 1956) or in the nerve fibre course (Rintelen 1969) may also prove significant The nature of the lesion may be a pressure or a pull on the nerve fibres in the often enormously distended chiasma and optic nerves or a vascular obstruction by compression or bending The great reversibility sometimes seen suggests that the vessels play a major role

Ophthalmoscopy

The classic and still most common finding is diffuse atrophy of the discs (Table IX) with sharply defined borders (so-called primary atrophy) but it should be stressed that this is a late sign (Kelly 1963) In accordance with the subjective complaint and the visual acuity findings the two discs often show some difference in degree of pallor Table IX summarizes the present and previous series Papilloedema rarely occurs It is a late sign which develops only when the intracranial pressure is increased (van der Hoeve 1940) The Foster Kennedy syndrome is also uncommon It was reported by Olivecrona (1927) Alajouanine et al (1934) Guillaumat (1937) Cushing & Eisenhardt (1938) Schlezinger et al (1946) Philippides et al (1953) Holub (1956) Cassinari & Bernasconi (1957) Guillaume et al (1957) Rucker & Kearns (1961) El Banhawy & El Nadi (1962) Vérin (1963) and Hugonnier et al (1968) making a total of 16 cases Papilloedema was not found among the cases

TABLE IX

Pre operative ophthalmoscopic findings in suprasellar meningioma

	Cushing & Eisenhardt 1929 1938	Guillaumat 1937	Holub 1956	Grant & Hedges 1956	Olivecrona Vérin 1963	Present series 1973
Both discs normal	–	–	3	3	8	6
One disc normal the other atrophic	2	3	–	3	28	13
Both discs atrophic	21	13	20	24	41	12
One disc oedematous the other atrophic	1	3	1	–	4	–
Bilateral papilloedema	2 (atrophic)	2	–	–	2	–
No information	2	1 (myopia)	–	–	–	–

From Guillaumat p 150 These figures are not quite identical with those given in the text by the author

of the present series Among the 12 anterior suprasellar meningiomata of Goutelle et al (1970), five showed papilloedema one with contralateral optic atrophy

The retinal arteries are generally stated to be normal (e g Newell & Beaman 1958) A few authors however described attenuated arteries (Guttmann & Spatz 1929) which became dilated after operation (Marx & Boeve 1932, Coulonjou et al 1950) At the same time the colour of the disc was said to change A return to normal of the disc vascularization after operation was reported by Martel et al (1931) Grant & Hedges (1956) in a series of 30 patients reported that seven with optic atrophy in one or both eyes before operation were said to have normal discs postoperatively These few communications emphasize the significance of vascular obliteration in the pathogenesis of visual defects In the present series vascular changes were not considered in particular and no further clinical information on this question can be supplied

Other neurological findings

A suprasellar meningioma characteristically presents with only neuro-ophthalmological symptoms The occurrence of *headache* is summarized in Table VI In some publications a large percentage of the patients are reported to have complained of headache (e g Guillaumat 1937 Grant & Hedges 1956 Verin 1963), whereas in others this symptom is not given much attention (e g Guttmann & Spatz 1929 Henderson 1938 Meadows 1949 Jane & McKissock 1962) The headache at least does not seem to be of a characteristic nature or localization, and quite often it seems unrelated to the tumour unless it is a sign of increased intracranial pressure In intrasellar tumours headache appears more regularly

Symptoms from the hypophysis and the hypothalamus are mentioned as late phenomena (Cushing & Eisenhardt 1929 Velter 1936 Guillaumat 1937) Cases demonstrating this are found in the early literature (Stewart 1899 Guttmann & Spatz 1929) Pre operative endocrine symptoms were particularly emphasized by Verin (1963) who observed such symptoms in 15 of 83 cases Grant & Hedges (1956) and Newell & Beaman (1958) also reported possible pituitary involvement One of Guillaumat s patients (No 6) had undergone operation for a pituitary adenoma 5 years before the symptomatic onset of the meningioma Although there are usually no symptoms and signs from the hypothalamus Lundberg & Hugosson (1966) showed that the metopirone test may be positive in suprasellar meningioma indicating a pressure on the anterior part of the hypothalamus

Anosmia an important symptom in olfactory meningioma is rarely found in *suprasellar meningioma It was not found in any of our 31 cases and it is reported* only in a few instances in the literature (Holmes & Sargent 1927, Schlezinger et al 1946 Bardram & Møller 1952 Holub 1956 Grant & Hedges 1956) except in the series of Guillaumat (1937 8 of 22 cases) Guillaume et al (1957, 5 of 21 cases) and Verin (1963 11 of 83 cases) It is of interest to note that among the 12 cases of anterior suprasellar meningioma reported by Goutelle et al (1970), anosmia did not occur

Mental changes especially a frontal syndrome are rare except again in the series of Guillaumat which is evidently composed of very late cases (tumour weight 10 100 g) Pre-operative epilepsy mental changes hemiparesis vertigo facial paresis exophthalmos and trigeminal affection should all be regarded as late signs occurring only in neglected cases

According to Velter (1936) the cerebrospinal fluid is always normal Stern (1950) reported that lumbar *spinal protein* was normal in suprasellar but increased in ethmoidal and sphenoidal meningiomata This difference probably only reflects the fact that suprasellar tumours produce symptoms while they are still very small Otherwise information in the literature on this point is scant In our series CSF analyses were performed only in a few cases

Lesions which involve the hypothalamic region or cause hypopituitarism may be associated with *EEG abnormalities* (theta activity) (Tonnis et al 1953 Boselli & Jefferson 1957) As suprasellar meningiomata are accompanied by hypopituitarism and hypothalamic symptoms only late in the disease EEG changes are considered to be of no significance in the diagnosis

Influence of pregnancy

Bitemporal visual field defects may arise during pregnancy (Bonamour et al 1971) These defects according to Enoksson et al (1961) may be divided into a large group with temporal constrictions of a functional nature and a group of cases with chiasmal lesion

The symptoms of a suprasellar meningioma may appear or may be accelerated during a pregnancy Some remission after delivery is the rule Among the 160 women in Table V a relation to pregnancy was mentioned in 12 cases In the present series a relationship was noted in two cases (Nos 10 and 25) This problem has been given special attention in papers by Fischer (1931) Hagedoorn (1937) Coulonjou et al (1950) Weyand et al (1951) Bardram & Moller (1952) Bocci (1954) Migliavacca & Cassinari (1955) and Walsh (1957) The coincidence is also mentioned in the series reported by Holmes & Sargent (1927) (case 4) Cushing & Eisenhardt (1929) (case 11) Guillaumat (1937) (cases 7 and 13) and Weber (1965) It seems evident that pregnancy has a stimulant influence on the development of the tumour resulting either in accelerated growth (Cushing & Eisenhardt 1929 Fischer 1931) or merely in vascular engorgement and oedema (Weyand et al 1951)

Analysis of pre operative clinical findings – positive diagnosis

Several authors have been surprised by how little the patients are alarmed by their decreasing visual capability This tolerance to visual impairment is found also in pituitary adenoma (Lyle & Clover 1961 Elkington 1968) and may in some instances be due to the fact that the family doctor disregards the patient s trouble

Characteristically the visual loss begins in one eye and may for years remain unilateral Cases with the two eyes equally affected are rare (Guillaumat 1937) this was observed only once in the present series (case 16) The course of the visual deterioration is normally a gradual progression but it may occasionally be intermittent (Cushing & Eisenhardt 1938 Guillaumat 1937 Coulonjou et al 1950 Grant & Hedges 1956 Verin 1963 Hugonnier et al 1968)

The *duration of symptoms* may vary from less than one month (Table II No 12 Joy 1952 Verin 1963 case 3) to several years 37 years reported by Borel (1929) in an artist who was aware of a bitemporal dyschromatopsia and 38 years reported by Forster & Bouzarth (1967) are probably the longest histories In 14

TABLE X

Influence of age, sex, tumour size and histopathology on pre-operative history

	No	Average age years	Duration of history years	M/F	Tumour size L/S	Optic atrophy A/N	Average field score	Average effective VA
< 40	11	36.2	2.5	0/11	4/7	11/11	47 %	82 %
40–60	15	49.5	2.8	5/10	11/4	19/11	46 %	70 %
> 60	4	65.3	2.1	1/3	3/1	7/1	34 %	73 %
Women	24	45.3	2.9	–	13/11	30/18	44 %	72 %
Men	6	52.7	1.7	–	5/1	7/5	49 %	84 %
Large	18	48.2	3.1	5/13	–	25/11	42 %	68 %
Small	12	44.7	1.9	1/11	–	12/12	56 %	85 %
E	13	43.9	2.4	1/1	8/6	18/8	47 %	80 %
E + F	11	52.6	1.8	4/7	8/3	12/10	43 %	69 %
F	6	41.8	4.5	1/5	2/1	7/5	54 %	73 %

This table contains data for 30 patients from the present series. Case no. 20 is excluded as it was asymptomatic. The table is discussed on p. 36.

of the 22 patients of the present series, in whom failing vision was the initial symptom, the duration of this symptom was less than one year. In only three cases was it longer than 5 years. Average figures are given in Table X. In 17 of the 30 cases of Grant & Hedges (1956) the length of history was less than one year. In the series of Olivecrona (Verm 1963) 22 of 83 cases had a history of less than 1 year and 38 of less than 2 years. Some of our cases indicate that rapid progression may occur when the tumour develops under the optic nerve and compresses it against the foramen opticum.

Cases similar to pituitary apoplexy are not reported in suprasellar meningiomata. Pupillary anomalies other than those accounted for by the visual loss have not been reported.

The actual combination of the signs and symptoms of a suprasellar meningioma changes with the stage of development of the tumour and is probably best illustrated by some selected cases. Failing vision is the symptom which brings the patient to the ophthalmologist. At the first examination optic atrophy may or may not be present but later it is an obligate sign. Field defects are by far the most important in the early diagnosis of a suprasellar meningioma and there is no doubt that several patients are coming to operation at a too advanced stage because the ophthalmologist did not examine the visual field at the early consultation of the patient. Early central scotomata were reported by Hagedorn (1937) and Alport (1951) and were especially emphasized by Schlezinger et al. (1946), Meadows (1949), Bardram & Møller (1952), Lyle & Clover (1961) and Kelly (1963). An early scotoma may disappear (Bardram & Møller 1952). However, it returns and in combination with a peripheral defect it was said by Schlezinger et al. to be particularly characteristic of a meningioma. Although this sequence was not observed in the present series, we encountered several examples of the combination

of central and peripheral defects (Figs 5 & 7) The peripheral defects make a neuritis improbable and the combination does certainly arouse strong suspicion of a tumour The fully developed bitemporal hemianopia is a late sign and to day it must be considered too late if the diagnosis is not made until the classic picture of optic nerve atrophy and bitemporal hemianopia in a patient with a normal sella has developed Although optic nerve and chiasma compression has been known for 150 years patients are still blinded from this (Kelly 1963)

Case 25 34 year old woman Monosymptomatic failing vision for 1 year Progressively developing irregular visual field defects Right disc atrophic left normal Plain radiography and pneumography estimated to be normal Operation 10 g meningioma from the tuberculum sellae Postoperative complete recovery in the best eye 3 years follow up

A woman 34 years of age in 1968 who for about 1 year had noticed failing vision in the right eye and for the last 6 months also in the left eye An eye examination 8 years previously was said to have shown some visual impairment in the right eye but no subjective complaints were present at that time The visual impairment started shortly after the patient's third delivery in 1967 when she noticed a shadow in the upper half of the right visual field The patient consulted an ophthalmologist and was told that the visual defect in the right eye was congenital Two more ophthalmologists gave the same answer When the left eye was affected she sought a fourth ophthalmologist who referred her to hospital

On admission (February 1968) visual acuity was RE counting of fingers LE 0 67 Ophthalmoscopy showed an atrophic right optic disc the left was normal Perimetry (Fig 6) showed bilateral defects Plain radiography of the skull and pneumo-encephalography showed nothing abnormal but reappraisal disclosed hyperostotic thickening of the presellar area and in the pneumogram elevation of the anterior part of the third ventricle On readmission in June 1968 visual acuity was RE hand movements LE 0 4 Ophthalmoscopy showed an atrophic right and a slightly pale left disc The field defects had definitely progressed (Fig 6) There were still no other neurological symptoms or signs in particular no headache and a normal sense of smell Exploratory craniotomy was decided although from the presumed negative pneumography the tentative pre operative diagnosis was one of chiasmal arachnoiditis

Operation (June 1968 Malmros) Through a small right anterior craniotomy the chiasmal region was exposed after puncture of the lateral ventricle A small typical meningioma from the tuberculum sellae elevating the right optic nerve was removed in pieces The tumour attachment was hyperostotic and profuse bleeding from this was controlled by coagulation The tumour covered the sellar diaphragm and pressed the chiasma backwards and somewhat downwards Tumour weight approx 6 g Histological diagnosis endotheliomatous meningioma Postoperative course uneventful

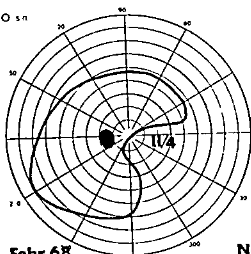
Follow up Examination 5 days after the operation showed visual acuity RE hand movements LE 0 67 Right disc atrophic left normal Perimetry (Fig 6) probably unchanged in the right eye normal in the left eye After 3 months vision in RE hand movements LE 1 0 Discs unchanged Perimetry unchanged (Fig 6)

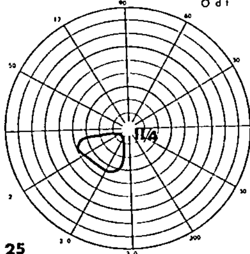
Re-examination 3 years later (Aug 1971) vision in RE hand movements LE 1 0 emmetropia Right disc atrophic with narrow arteries left normal Perimetry of the right eye (Fig 6) showed unchanged conditions left eye was normal There were no complaints in particular no headache Neurological examination showed nothing abnormal Plain radiography of the skull showed some hyperostosis of the planum sphenoidale otherwise nothing abnormal

Case 12 60 year old woman Short history early diagnosis Cure and possible recurrence after 16 years

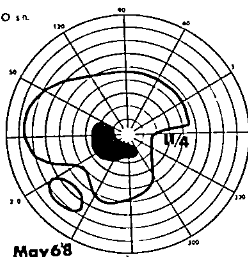
A 60-year-old housewife who for one month had experienced failing vision in the left eye Examination 7 years earlier had shown normal visual acuity in both eyes Now the same ophthalmologist found visual acuity 0 15 in the right eye and 0 33 in the left eye a pale right optic disc and bitemporal central visual field defects The patient was immediately referred to hospital

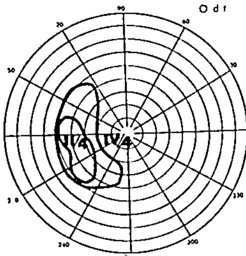
On admission (June 1955) the visual acuity was RE 0 5 + 1 00 sph and LE 0 33 + 1 00 sph. Ophthalmoscopy showed that the discs were somewhat but not definitely atrophic with no convincing difference between the right and the left Perimetry showed small bitemporal

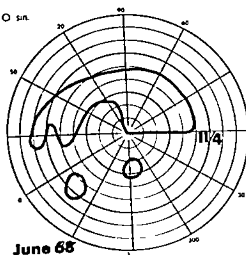

O s.n.
II/4
Febr 68

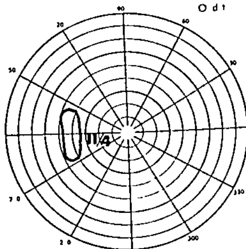

O d t
II/4

No 25


O s.n.
II/4
May 68


O d t
II/4
IV/4


O s.n.
II/4
June 68


O d t
II/4

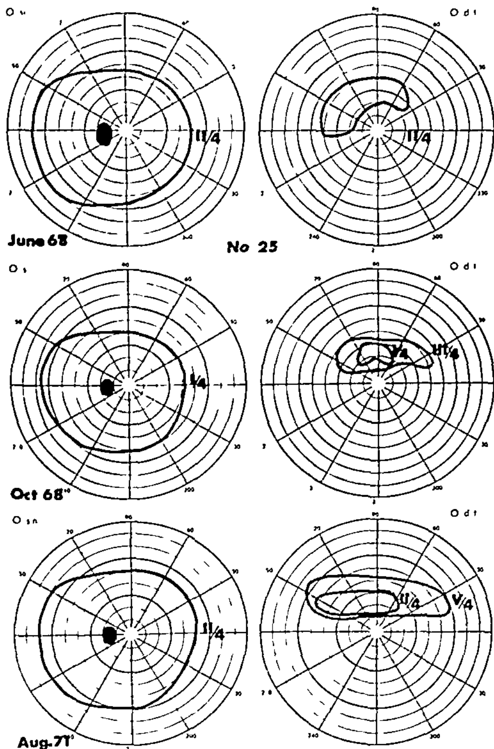
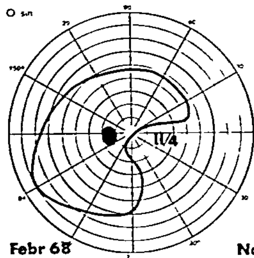
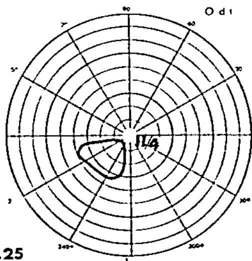
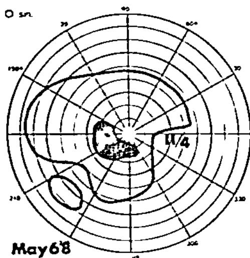
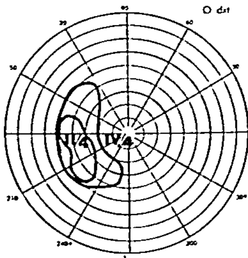
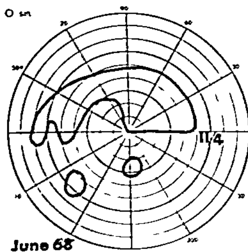
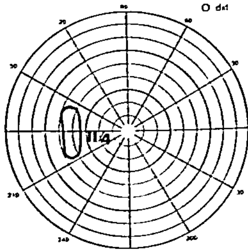


Fig 6 A sequence of visual field findings in a patient with a suprasellar meningioma (No 25) For details see case history The patient was operated on in June 1968 The first chart from this month is pre-operative the second postoperative


O sin
II/4
Febr 68

O d1
II/4
No. 25

O sin
II/4
May 68

O dxt
II/4
IV/4

O sin
II/4
June 68

O dxt
II/4

On admission (Nov 1946) visual acuity was RE no light perception LE 1 0 Ophthalmoscopy showed a diffusely atrophic right disc the left was normal The retinal vessels were normal Perimetry showed a regular left temporal hemianopia Ocular movements and corneal sensibility were normal The pupils reacted in accordance with the right optic atrophy A neurological examination showed a completely healthy woman except for a doubtful right hyposmia X ray examination showed a normal sella no areas of destruction or abnormal calcifications Right carotid angiography showed a depression of the upper end of the carotid artery and no filling of the right anterior cerebral and anterior communicating artery Pneumography showed elevation and displacement of the left anterior horn of the lateral ventricle suggesting a large suprasellar tumour

Operation (Nov 1946 Malmros) The chiasma region was exposed through a right anterior craniotomy The right optic nerve was displaced backwards and downwards and was surrounded by the tumour The tumour base was on the anterior part of the sellar diaphragm and the dura just anterior to this The tumour extended behind the chiasma and was removed in pieces Tumour weight 40 g Histological diagnosis endotheliomatous meningioma The postoperative course was uneventful

Follow up Ophthalmological examination in the postoperative period showed a minor change in the visual field otherwise unchanged conditions At an examination 12 years after operation the situation was found unchanged and 24 years after (Aug 1971) visual acuity was RE 0 5 LE no light perception Both discs atrophic Perimetry showed a temporal hemianopia in the right eye unchanged since the operation

Case 14 39 year-old woman Periocular pain followed by reduced vision in the left eye Negative angiographies and pneumoencephalography 4 3 g meningioma removed from the tuberculum sellae No recurrence after 15 years

A woman 39 years of age in 1956 who one year previously had noticed pain behind the eyes mainly the left For the next few months there were episodes of dim vision in the left eye lasting for about half an hour Gradually the visual loss became permanent Examination revealed a temporal paracentral scotoma recorded as shown in Fig 7 5 months after the onset of the disease After one year a temporal hemianopia was found in the left eye (Fig 7) the right still being perfectly normal During the last year there had been a constant headache localized to the vertex of the skull The sense of smell was normal

On admission (Sept 1956) visual acuity was RE 1 0 LE counting of fingers Ophthalmoscopy showed a normal right disc and a diffusely pale left disc The vessels were normal Perimetry showed only upper nasal quadrant retained in the left eye in the right a questionable upper temporal defect only demonstrable by red object Plain X ray films of the skull showed nothing abnormal right and left carotid angiography and pneumo-encephalography did not either reveal any abnormalities

Operation (Oct 1956 Malmros) through a left anterior craniotomy revealed a typical meningioma elevating the left optic nerve The tumour base was at the tuberculum sellae

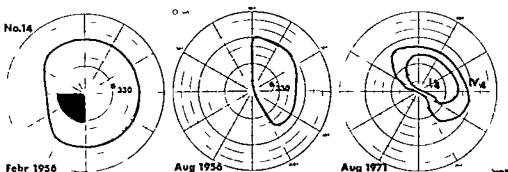


Fig 7 Sequence of visual field findings in a patient with a suprasellar meningioma (No 14) All three charts are from the left eye the right eye was normal Operation was performed in October 1956 For details see case history

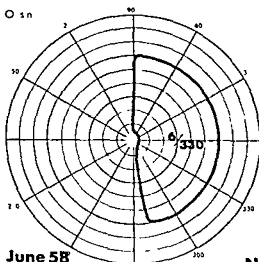
measuring 5x8 mm the tumour was removed in one piece weight 4 3 g Postoperative course was uneventful Histological examination showed a fibrillar meningioma.

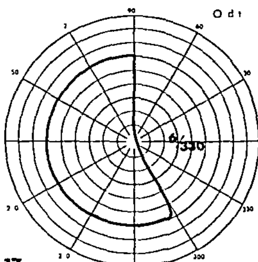
Follow up Examination immediately after operation and 1 year later gave unchanged ophthalmological findings At the re examination after 15 years visual acuity was RE 1 0 LE counting of fingers Right disc normal left atrophic Vessels normal Perimetry showed some improvement in the left eye (Fig 7) the right was normal No abnormal neurological findings

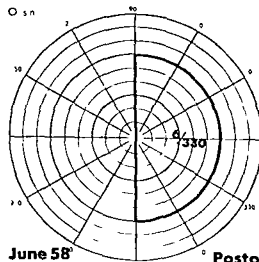
Case 17 39 year-old woman Bitemporal hemianopia after 7 months of visual complaints Removal of a 6 g meningioma with attachment anterior to the sella

39 year-old woman (1958) who for 7 months had observed a mist before both eyes gradually progressing 4 months ago on a single occasion there was diplopia for distant objects Later she noted a temporal constriction of the visual fields After 5 months (April 1958) she consulted an ophthalmologist who found the vision in RE> 1 0 LE 0 1 Left disc pale bitemporal hemianopia The patient was referred to hospital

On admission (June 1958) the visual acuity was RE 1 0 LE 0 1 Ocular movements nor mal no protrusion Left disc pale but with normal vessels right normal Perimetry bitemporal







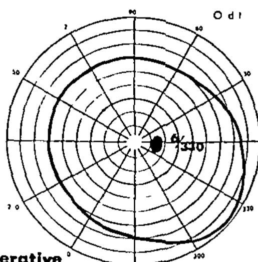


Fig 8 Pre and postoperative visual fields in a patient with a suprasellar meningioma (No 17) For details see case history

hemianopia (Fig 8) Neurological examination showed nothing abnormal The patient was obese but without signs of dyspituitarism A plain radiograph of the skull revealed hyperostosis anterior to the normal sella turcica Right and left carotid angiographies showed that the anterior cerebral arteries were elevated by a vascularized 2x2 cm large process supplied from the anterior cerebral and the ophthalmic artery (Fig 13) The pre-operative diagnosis was one of suprasellar meningioma Before operation visual acuity in the left eye was reduced to hand movements Right eye and perimetry were unaltered

Operation (June 1958 Malmros) Through a left anterior craniotomy a typical suprasellar meningioma was exposed It was removed in pieces The right optic nerve was displaced backwards and the tumour had produced a cavity under the chiasma and the anterior part of the third ventricle The attachment in the area around the tuberculum sellae was densely coagulated Tumour weight approx 6 g The infundibulum was undamaged Histological diagnosis endotheliomatous meningioma Uneventful postoperative course

Follow up Visual acuity 4 days after operation was RE 1 0 LE 0 1 Ophthalmoscopy unchanged Perimetry see Fig 8 Examinations after 7 and 14 months showed completely unchanged conditions

Case 18 Second tumour Failing vision partial removal of tumour from the diaphragma sellae behind the infundibulum Postoperative hypopituitarism

October 1965 8 years after her first symptoms and 7½ years after the operation the patient noted reading difficulties An ophthalmologist prescribed glasses After 3 months she consulted another ophthalmologist who found visual acuity RE 0 33 LE no light perception and referred her to hospital

On admission (February 1966) the visual acuity was RE 0 4 LE *no light perception* 15 divergence of the left eye, movements unrestricted. Right disc slightly pale left atrophic Field examination disclosed upper temporal defect. Neurological examination showed nothing abnormal The patient was obese without dyspituitarism Menopause ? years previously Plain X ray film showed nothing abnormal Bilateral carotid angiography revealed only a slight elevation of the anterior cerebral vessels

Operation (March 1966 Malmros) The chiasmal region was exposed through a right anterior craniotomy The right optic nerve and the infundibulum elevated by a large tumour The tumour infiltrated the left optic nerve and was adherent to the left carotid artery The tumour was removed in pieces its base on the diaphragma sellae was coagulated Haemor

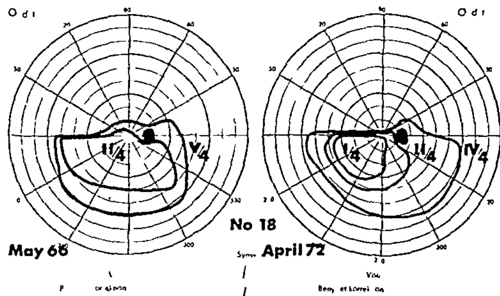


Fig 9 Postoperative visual fields from right eye of the same patient as in Fig 8 (No 18) The left eye was blind

rhage from the left carotid artery was controlled by application of muscle pieces Probably som tumour tissue was left under the right carotid artery On the day of operation the patient was given Decadrone 4 mg x 5 the following 3 days 4 mg x 6 The dose was then gradually reduced until it was withdrawn on the 10th day Immediately after the operation there was diabetes insipidus which was controlled by insipidin The patient was tired apathic with low blood pressure (105/90 90/70), vomiting and diarrhoea Ventriculography showed nothing abnormal The internist found definite signs of pituitary insufficiency and cortisone treatment was resumed

Follow up Examination 3 weeks after the operation RE 0 4 LE no light perception Right disc pale left atrophic Perimetry see Fig 9 Examination 6 months later (Nov 1966) RE 0 67 LE no light perception Ophthalmoscopy and perimetry unaltered The patient was tired Examination 6 years later (April 1972) showed RE 1 00 LE no light perception Right disc pale left atrophic Perimetry unchanged (Fig 9)

The *age distribution* of patients with suprasellar meningioma was shown in Fig 2, with an average age of 40 7 years that of our own patients, with an average age of 46 7 years appeared from Fig 3 The wide age range immediately raises the question whether differences exist between young and old patients The survey of the cases given in Table V does not support any such suspicion A division of our patients into groups below 40 between 40 and 60 and above 60 years of age at the first symptom (Table X) shows that the length of history before operation was 2 5 2 8 and 2 1 years respectively The differences in the length of history are not statistically significant All patients below 40 were women and this group also contains many of the small tumours Optic atrophy seems to occur more frequently with increasing age In the youngest group 11 of 22 discs were atrophic as compared with 7 of 8 discs (88 %) in the oldest group This difference possibly reflects a greater vulnerability of the *nutrition, accordant with increasing arteriosclerosis* Similarly the average effective visual acuity and average field score showed a decreasing tendency with increasing age

Suprasellar meningiomata show a statistically significant female preponderance It may therefore be asked if the clinical course is *different in the two sexes* This question has not been considered in the literature In the present series the average age for 24 women at the onset of symptoms was 45 3 years, for 6 men it was 52 7 years The average length of the history was 2 5 years in the entire series In 24 women the duration of symptoms was 2 9 years (34 months), in 6 men only 1 7 years (20 months) Among the men, one had had symptoms for 84 months while in the remaining five the duration of the symptoms was only 8 months This might suggest that the disease runs a shorter course in men than in women The difference is however not statistically significant As regards tumour size optic atrophy and average field score no differences exist between men and women The average effective visual acuity is somewhat higher in men than in women

Jane & McKissock (1962) divided their series into *large and small tumours* The small tumours had a diameter of less than 3 cm corresponding to a weight of 5 6 g The large tumours had an average length of history of 26 months (2 2 years) and an average age at operation of 49 8 years For the small tumours, the average duration was 36 4 months (3 0 years) and the average age at operation 44 0 years In our series the duration of symptoms was 37 2 months for the large and 22 8 months for the small tumours The average age of the patients at the onset of symptoms was 48 2 and 44 7 years respectively for large and small tumours Thus both series suggest that the small tumours occur in younger persons, while the

lengths of history are mutually inconsistent in the two series preventing any suggestions

The tumours in the present series have been grouped *histopathologically* in accordance with Russell & Rubinstein (1971) as endotheliomatous (E) fibrillar (F) and transitional (E + F) Table X summarizes the relationship between the pathological structure and the clinical course There appear to be no evident differences between the three groups except for the length of history of 4 5 years for fibrillar meningiomata This figure is however caused by the earliest cases especially case 1 which to-day would have been subjected to operation at an earlier stage of the disease

Exact localization of the suprasellar meningioma

The meningiomata originate from the arachnoidal cells in relation to the villous processes of the venous sinuses (Russell & Rubinstein 1971) As the sinuses surround the hypophysis more or less like a ring under the diaphragma sellae the meningioma may arise at the tuberculum sellae laterally under the optic nerve or even posteriorly behind the infundibulum in front of the dorsum sellae Cushing although he used the name suprasellar meningioma considered the tuberculum sellae to be the site of origin In many of the cases reported the exact area of attachment is not specified and in another large group the origin is said to be the tuberculum sellae probably just because the tumour is named a tuberculum sellae meningioma Of the many cases in which the localization is carefully described the majority originate from the tuberculum sellae area (tuberculum sellae sulcus chiasmatis limbus sphenoidalis) Other areas may be the jugum *sphenoidale (Goutelle et al 1970* Table II case 21) the anterior clinoid process (Table II case 9) near the optic foramen (Table II case 5) or the diaphragma sellae (Holmes & Sargent 1927 Guillaumat 1937 Meadows 1949 Busch & Mahneke 1954 Olivecrona 1967 Guiot et al 1970 Table II cases 4 18 and 30) A meningioma arising from the diaphragma sellae may grow behind the infundibulum and behind the chiasma the retrochiasmal suprasellar meningiomata of Guiot et al (Table II case 18) This localization apparently tends to give a more varied symptomatology with oculomotor paresis and pituitary insufficiency

DIFFERENTIAL DIAGNOSIS

The problems involved in differential diagnosis are entirely different in the early and in the late phase The practising ophthalmologist, among the numerous causes of failing vision has to catch the suprasellar meningioma, whereas in the neuro surgical department the problem more often is to differentiate between the various causes of the chiasmal syndrome In an ordinary practice the ophthalmologist can not expect to meet a suprasellar meningioma more than once or twice in his life whereas the neurosurgeon will meet this disorder 10 20 times as often

The common causes of the chiasmal syndrome are pituitary adenomata and craniopharyngiomata In the early diagnosis retrobulbar neuritis probably presents the greatest differential diagnostic problem

Problems in the early diagnosis

Failing vision no optic atrophy In the presence of monosymptomatic and uni lateral failing vision where the only subjective complaint is dim vision or a haze or mist before the eye retrobulbar neuritis with its various possible causes should be considered A history of acute onset and retrobulbar pain at movements of the eye may be helpful although periocular pain, as we have seen, has been reported in suprasellar meningioma Bilateral failing vision may also be caused by retrobulbar neuritis (Hierons & Lyle 1959) A retinal macular disease should always be looked for particularly a central serous retinopathy and the possibility of vitreous opacities or vitreous collapse must also be borne in mind

Failing vision and optic atrophy When optic atrophy is present or develops postneuritic atrophy must be considered Glaucoma also, has to be excluded especially if some excavation of the disc is present The progress of field defects is more rapid in meningioma than in glaucoma (Newell & Beaman 1958) Ischaemic optic neuropathy (giant cell arteritis or arteriosclerosis) characteristically has an acute or hyperacute onset and the retinal vessels are narrow and/or sclerotic Cranial dyssynostosis may be the cause of optic atrophy (Bertelsen 1958)

The group of retinal atrophies are characterized by a yellow colour of the disc and by thread thin arteries whereas peripheral pigmentations may be missing If macular disease is present this may be the cause of some atrophy mainly temporal (Marx & Boeve 1932) As regards hereditary optic atrophies (Leber Kjer Behr) a family history will be of interest Walsh et al (1956) encountered a suprasellar meningioma in an individual considered for 10 years to have had Leber s optic

atrophy Tabetic atrophy and post intoxication atrophies also have to be considered (methanol tobacco ethanol quinine chloramphenicol tuberculostatics etc)

Traumatic optic atrophy is fairly common (1 5 per cent of all head injuries Russell 1940 Turner 1943) Frontal or facial injuries may cause optochiasmatic or chiasmatic symptoms (Hartmann 1945 Hughes 1962 Meyer 1965) either by stretching (Logan & Gordon 1967) by sagittal disruption of the chiasma (Østerberg 1938 Bruun Laursen 1971) or by interference with the blood supply to the central sagittal region of the chiasma The visual field defect encountered may mimic those seen in suprasellar meningioma (Hughes 1962)

Visual field defects Field defects of the bitemporal type greatly reduce the diagnostic possibilities a chiasmal syndrome then being probable It should however, always be borne in mind that nasal myopia with a posterior staphyloma (Ruse 1966 1970) may give rise to bitemporal defects Myopia and usually an inverse origin of the retinal vessels are suggestive Field examination with various corrective lenses or ultrasonography (Fledelius 1970) will solve the problem Finally it may be worth remembering that drusen of the optic disc may give various types of field defects or obscure the real nature of the field defects (Rucker & Kearns 1961)

Causes of the chiasmal syndrome

These have been extensively treated by several authors e g Favory (1926) Christiansen (1927) Olivecrona (1938) Walsh et al (1956), Walker (1962) Weber (1965)

Intrasellar tumours Pituitary adenomata are by far the most common cause of the chiasmal syndrome (Smith 1965 Weber 1965 Ruse 1970) but intrasellar craniopharyngioma and metastases (Weber 1965) also occur The intrasellar tumours are diagnosed by radiography which usually shows an enlargement of the sella Clinically they are attended by hypophyso-hypothalamic symptoms and the eosinophilic by headache which is not typical of the chromophobe adenoma (Jefferson 1937) Pituitary adeomata may by lateral extension give oculomotor pareses (Bardram 1949 Huber 1956 Elkington 1968) and possibly exophthalmos symptoms seen only exceptionally if ever in suprasellar meningioma Pituitary adenomata are approximately equally common in men and women (Elkington 1968)

Extrasellar tumours Among these the most frequent is the craniopharyngioma which may generally be differentiated from the meningioma by its occurrence in young patients in whom they produce symptoms of increased intracranial pressure as well as from the hypophysis and hypothalamus The craniopharyngioma is characterized by fluctuations in visual acuity according to varying fluid contents (Smith 1965) When they occur in adults often past middle age they may to some extent simulate a meningioma although a certain degree of hypopituitarism is generally present Plain radiography often reveals a calcification in the tumour

Although from a clinical point of view the suprasellar meningioma represents a well delineated disorder other juxtachiasmatic meningiomata may give similar symptoms Ethmoidal meningiomata may be impossible to differentiate from the suprasellar variety simply because there is no sharp line of demarcation between the two Twelve cases of meningioma showing a transitional form were described by Goutelle et al (1970) under the name of anterior suprasellar meningioma However ophthalmological symptoms develop only when the tumour has attained a considerable size General symptoms including signs of increased intracranial pres

sure frontal symptoms and possibly also the Foster Kennedy syndrome are therefore present Anosmia is an important differential diagnostic sign Among the 26 patients with ethmoidal meningioma in our series (Table I), 12 complained of failing vision Eight of these had optic atrophy and might be confused clinically with a suprasellar meningioma It should be noted that four of these cases showed scotomatous defects one revealed altitudinal defects one peripheral bitemporal defects, and one had one blind eye and one with a normal field while in the last case no field examination was made Central scotomata in ethmoidal and in medial fossa meningiomata were emphasized by Westby (1963)

The following cases showed transitional forms

Case G 28944 Ethmoidal meningioma simulating a suprasellar meningioma
A 66 year old woman who 5 years previously had had a short period (a few days) of bilaterally reduced vision followed by full restitution During the last 2 3 years vision again began to fail For the last 6 months completely abolished sense of smell

On admission visual acuity was 0 67 + 2 50 sph in both eyes The optic discs were atrophic with sharp borders Retinal arteries were attenuated and changing in calibre Perimetry showed bilateral paracentral scotomata (Fig 10) Right carotid angiography showed an elevation of the first part of both anterior cerebral arteries

Operation (Malmros) disclosed a large (hen egg sized) globular meningioma originating from a large area in the midline extending from the cribriform lamina to the tuberculum sellae The right optic nerve and the chiasma were pressed backwards and downwards The tumour was growing out upon the sellar diaphragm Histological examination showed a fibrillar and endotheliomatous meningioma

Follow up After 6 months the optic atrophy and scotomata were unchanged

Case G 34581 Ethmoidal meningioma simulating a suprasellar meningioma
A 60 year old woman with failing vision for 6 months and for some years decreasing sense of smell

On admission vision in RE was 0 67 LE light perception in the two lower quadrants The right optic disc was normal the left slightly atrophic Perimetry of the right eye showed a central scotoma. Left carotid angiography showed a tumour in the anterior fossa

Operation (Malmros) revealed a very large tumour originating from the area around and behind the crista galli The tumour extended beneath the chiasma and was adherent to the area around the tuberculum and the diaphragma sellae Histological examination fibrillar and endotheliomatous meningioma.

Follow up Four years later vision in RE was 1 0 LE hand movements in front of the eye Right optic disc normal left atrophic Normal perimetry in the right eye

If anosmia had not been present the scant medical histories would have suggested suprasellar meningioma The cases reported above do not support the statement of Guillaumat (1937) that transitional forms between suprasellar and ethmoidal meningiomata run a short course when they have grown so large as to become clinically manifest Meningiomata arising from the inner third of the sphenoid ridge may present with unilateral failure of vision and optic atrophy (Cushing & Eisenhardt 1938 Walsh et al 1956 Newell & Beaman 1958) as illustrated by the following case

Case G 1970 Sphenoidal ridge meningioma simulating a suprasellar meningioma
A 66 year-old woman with failing vision of the right eye for 10 years No progression during the last two years During the last year somnolence failing memory and gradually increasing protrusion of the right eye

On admission RE finger counting before the eye LE 1 0 The right optic disc was atrophic the left normal Perimetry showed a central scotoma in the right eye the left field

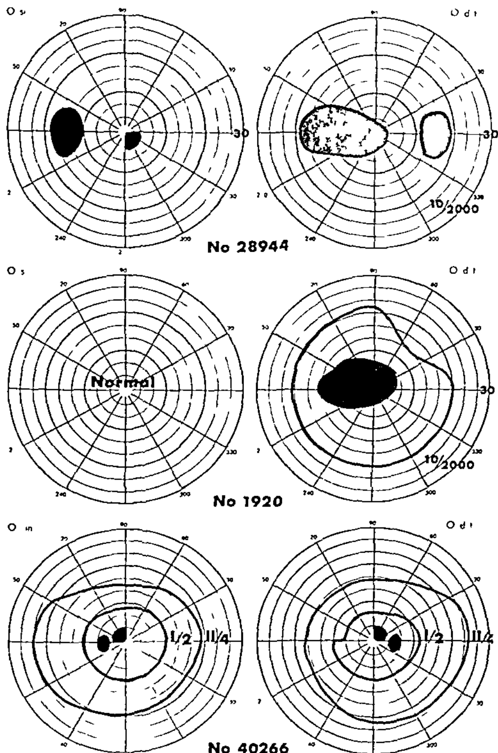


Fig 10 Visual field findings in patients with ethmoidal meningioma (No 28944) sphenoidal ridge meningioma (No 1920) and optochiasmatic arachnoiditis (No 40266) For details see case histories

was normal (Fig 10) *Slight protrusion of the right eye with somewhat reduced horizontal movements* Corneal sensibility and pupils were normal

Neurological examination including sense of smell was normal X ray of the skull Hyperostosis of the sphenoidal wing suggestive of an en plaque meningioma Right carotid angiography normal intracranial vessels

Operation (Malmros) revealed a meningioma of the sphenoid ridge extending backwards into the middle cranial fossa *The tumour reached the optic foramen The tumour and the* dura were removed Postoperative course uneventful Histological diagnosis endotheliomatous meningioma

Follow up Postoperative visual acuity and field examination were unchanged and when heard of 8 years later the condition was stationary

Advanced stage symptoms of sphenoidal meningiomata include proptosis, diplopia periocular pain papilloedema and corneal hypaesthesia (David & Hartmann 1935 Kearns & Wagner 1953) These facts are illustrated in Table I

Meningiomata arising in the bony canal of the optic nerve are rare

Case G 20552 Meningioma of the left optic foramen simulating suprasellar meningioma

A woman 69 years of age who for 6 months had noted a fog before the left eye

On admission vision in RE 1 0 LE 0 2 Right disc normal left atrophic with attenuated retinal vessels

Perimetry was normal in the right eye in the left there was a temporal hemianopia X ray examination of the skull including the optic foramina and laminography of the sella turcica showed *nothing abnormal Right carotid angiography and pneumography were also normal*

Operation (Nov 1957 Malmros) Left craniotomy Left optic nerve elevated and compressed at the optic foramen by a small meningioma (8 x 5 x 3 mm weight 0 1 g) which was situated below and in front of the nerve It was removed in one piece The attachment was on the medial wall of the optic canal Histological diagnosis endotheliomatous meningioma Postoperative course uneventful

Follow up After 4 and 10 months vision in RE normal LE no light perception white disc

The patient died 10 months after the operation from arteriosclerosis and bronchopneumonia

A meningioma from the optic canal will probably often be diagnosed by an en larged optic foramen (Blatt & Athanasiu 1958) This may however, also be caused by a suprasellar meningioma as illustrated by case 16 in the present series and reported also by Guillaumat (1937) Cassinari & Bernasconi (1957), Passerini & Cecchini (1962) and Lombardi (1967) (Table XI)

Intracranial aneurysms mainly those localized to the supraclinoid part of the ca rotid artery the anterior cerebral or anterior communicating artery may present with uniocular visual loss and visual field defects Infraclinoid aneurysms involve other structures notably the oculomotor nerves Carotid angiography will reveal most aneurysms

Rare tumours which may give chiasmal symptoms are chordomata (Martel Monbrun & Guillaume 1931) ectopic pinealomata (Weber 1965, Rubin & Kramer 1965 Simson et al 1968) and epidermoid tumours (Farnarier & Sedan 1969) the latter appearing in young individuals and often showing enlarged optic foramina (Olivecrona 1938) Another possibility is a rhinopharyngeal tumour, especially a carcinoma from the sphenoid sinus seen in patients past middle age (Godtfredsen 1944) Tumours from the cavernous sinus and gliomata from the third ventricle (Learmonth et al 1931 Jefferson 1945) may also give rise to similar symptoms The latter generally run a short course with hypothalamic symptoms Jefferson (1945) described this in a supra optic syndrome including bitemporal hemianopia

polyuria lethargy and diminished general body activity Frontal lobe gliomata (Jefferson 1945) and distant tumours notably in the posterior fossa by dilation of the third ventricle, may cause bitemporal hemianopia (Walsh et al 1956 Walsh & Gass 1960) Gliomata from the optic nerves and the chiasma must also be remembered (Grote 1964 Glaser et al 1971) Signs of Recklinghausen s disease are sometimes present, and the optic foramen is often enlarged The visual field defects are very irregular Finally suprasellar metastatic tissue may occur probably as an extension of a pituitary metastasis (Scatliff & Bull 1945) Clinically metastases may be characterized by a history of primary malignancy

Other lesions Optochiasmatic arachnoiditis is a disease which is still of an obscure nature (Jacquemin & Frippiat 1969) Until recently its actual existence was doubted (Walsh et al 1956) It was extensively studied by Bollack et al (1937) and Hartmann (1945) Clinically it may simulate a meningioma (Coulonjou et al 1950) as illustrated by the following case

Case G 40966 Optochiasmatic arachnoiditis simulating supra ellar meningioma
A 48 year-old woman who for 18 months had noticed failing vision with progression particular ly during the last 6 months There were no other complaints

On admission vision in RE 0 5 LE 0 67 Optic discs were normal Visual field examination showed bitemporal paracentral scotomata (Fig 10) Eye movements pupils and corneal sensibility were normal Neurological examination and pneumo-encephalography showed nothing abnormal No diagnosis was obtained and steroid treatment was given for some time without effect. On re admission the ophthalmological findings were unchanged Right carotid angiography showed nothing abnormal Laminagraphy of the sellar region revealed some decalcification of the anterior clinoid processes otherwise nothing abnormal No remission occurred and exploration of the chiasmal region was found to be indicated an en plaque meningioma or an optochiasmatic arachnoiditis being the tentative diagnoses

Operation (Malmros) showed thickening of the arachnoid with vascularized bands o er the optic nerves and the chiasma. CSF was clear there were no cysts The thickened arachnoid was removed Histological examination showed se ere fibrosis The postoperative course was uneventful

Follow up Examination 6 months later showed vision in RE 0 67 LE 1 0 Optic discs and perimetry normal

As a rule the course of optochiasmatic arachnoiditis is more intermittent than that of suprasellar meningioma (Puech & Mahoudeau 1935) and the visual field defects more changing (Ronne 1938) Bitemporal field defects are the rule but homonymous horizontal binasal scotomatous or very irregular defects have been described (Velter 1936) the scotomatous defect being particular characteristic (Bollack et al 1937) Among 18 cases Jacquemin & Frippiat (1969) found 10 with papilloedema (called papillitis) and only one case of optic atrophy Others (e g Huber 1956) stated that optic atrophy is common The findings probably depend upon the stage at which the disease is being observed There may for a long time be a discrepancy between the reduced visual acuity and the ophthalmoscopic picture as known also from retrobulbar neuritis Optochiasmatic arachnoiditis is definitely more frequent in men (Hartmann 1945) The cause of optochiasmatic arachnoiditis is very often doubtful Pneumographically it may simulate a tumour because of cyst formations Hyposmia has also been reported

It has also been reported that an arteriosclerotic or tortuous internal carotid and ophthalmic artery may mimic a tumour compressing the optic nerve (Sunderland 1948 Meadows 1949 Mooney & McConnell 1949) or chiasma (Hilton & Hoyt

1976). Infectious processes, e.g. localized basal meningitis, multiple sclerosis (Weber 19[illegible]5), suppurative ethmoiditis or ostitis as well as tuberculosis (Schlesinger et al 1971) and syphilitic (Lavery 19[illegible]6) granulomata may occur.

RADIOLOGICAL FINDINGS

Radiography of the skull

The findings in suprasellar meningioma consist of reactive hyperostosis erosion of the clinoid processes calcification in the tumour (Fig 11), and enlargement of the optic foramen The reactive hyperostosis may involve a smaller or greater part of the presellar area with the planum sphenoidale limbus sphenoidalis sulcus chiasmatis and tuberculum sellae It may consist of hyperostotic thickening with increased density or be mound like having a spongy appearance The portion of the sinuses underlying the tumour may become enlarged and project intracranially blistering and opposite osteomatous changes may project into the sphenoidal sinus Lombardi (1967) found blistering' in 13 out of 31 cases and Tucker et al (1959) revealed osteoma in the sphenoidal sinus in 4 of 51 cases Calcifications in the tumour occurred in 6 7 % of 266 cases culled from various sources (Passerini & Cecchini 1962) They may be extensive or shell like Even in advanced cases the sella turcica will generally be of normal form and size although enlargement or flattening is sometimes described Available data are summarized in Table XI From this it may be concluded in accordance with Lombardi (1967) that in suprasellar meningioma the sellar region is rarely radiologically normal The higher incidence of positive findings in large than in small tumours is only reasonable It does not explain why in the earlier studies in which the tumours were often very large the diagnosis was not made radiologically Most likely the explanation is a better technique and a changed attitude to what can be considered pathological in this region Di Chiro & Lindgren (1952) described normal variations in the bone structures of the presellar region as seen in 100 plain radiographs They found that in nearly all cases a local thickening of the bone could be encountered in few cases even localized to the entire region but the thickening of the bone never exceeded 2 mm and the bone was sharply defined and its structure homogeneous It is probable that laminagraphy and stereoscopy will give still better results

In our series relevant radiological changes were encountered only in 4 of 31 patients pre-operatively However a reappraisal of 25 cases in which acceptable radiographs were available revealed relevant conspicuous changes in 14 while less relevant changes (e g decalcification of the dorsum sellae) were noted in 6 In 8 patients the X ray examinations were negative Among the 14 patients 13 showed hyperostotic changes in the presellar area 3 with blistering , and 2 patients had extensive calcifications in the tumour Among these tumours 12 were large and

1966). Infectious processes, e.g. localized basal meningitis, multiple sclerosis (Weber 19[illegible]), suppurative ethmoiditis or ostitis as well as tuberculous (Schlernitzauer et al 1971) and syphilitic ([illegible] 19[illegible]) granulomata may occur.

TABLE XI

Bone changes in suprasellar meningioma

Authors	Year	No of cases	Patients with changes		Abnormalities specified			
					Hyper ostosis	Erosions	Calcifi cation	Optic foramen
			No	%				
Guillaumat	1937	21	17	81	6	14	0	1
Cushing & Eisenhardt	1938	25	7	28	1	4	2	–
Davidoff & Epstein	1950	10			2	–	0	–
DiChiro & Lindgren	1952	45	23	51	23	–	3	–
Weyand & Camp	1954	51	33	65	28	13	8	–
Holub	1956	24			5	–	0	–
Grant & Hedges	1956	30	24	80	7	24	–	–
Cassinari & Bernasconi	1957	33	26	79	24	21	0	1
Tucker et al	*1959*	*51*	*43*	*85*	*26*	*36*	*4*	*0*
Passerini & Cerchini	1962	24	19	79	5	11	2	4
Bakay & Bean	1963	9	7	78	–	–	–	–
Lombardi	1967	34			20	9	5	2
Jane & McKissock	1962							
Small tumours		17	4	24	–	–	–	–
Large tumours		33	16	48	–	–	–	–
Present series (reappraisal)	1973							
Small tumours		10	4	40	2	2	0	0
Large tumours		15	13	86	11	4	2	0

Radiological findings in patients with suprasellar meningioma Data collected from the literature The figures from the present series are based on a reappraisal at the time of publication

2 small Histologically 12 tumours were classified as endotheliomatous (some with fibroblastic elements) while 2 were fibroblastic Among 6 fibroblastic tumours 2 revealed bone reactions so our series does not confirm the observations of Tucker et al (1959) that fibroblastic meningiomata never give rise to hyperostotic changes

Angiography

Anatomically suprasellar meningiomata are closely related to the anterior cerebral arteries and terminal portions of the internal carotid arteries Carotid angiography therefore is suitable for the investigation of lesions in this region (Driesen & Schmidt 1959 Jane & McKissock *1962* Bakay & Bean *1963* Feiring & Shapiro 1964)

Angiographic evidence of a suprasellar meningioma is a convex elevation of the anterior cerebral arteries with the anterior communicating artery often best seen in the antero-posterior view (Driesen & Schmidt 1959, El Banhawy & El Nadi 1962) (Fig 12) It must be added that the retrochiasmatic meningiomata of Guiot et al (1970) did not cause elevation of the anterior cerebral artery In the presence of a very large tumour the terminal portion of the internal carotid artery may be displaced laterally (Wickbom 1948 Driesen & Schmidt 1959 Tucker et al 1959) the so-called unfolding of the carotid siphon Additional findings are irregular

lumina of the internal carotid and anterior cerebral arteries abnormal arteries supplying the tumour filling of vessels in the tumour (blush or edge vessels) (Fig. 13) an avascular area or an abnormal venous filling probably due to arterio venous shunts within the vascular system of the tumour (Driesen & Schmidt 19(?) Tucker et al 19(?))

Quantitative information about the value of carotid angiography in the diagnosis of suprasellar meningiomata is sparse. The case material available is shown in Table XII. Carotid angiography will in most cases demonstrate the presence of a suprasellar meningioma.

From an analysis of our series it appears that tumours weighing more than ? g can be diagnosed by angiography while only ? of ? small tumours were demonstrated angiographically. This accords reasonably with the findings of Udvarhelyi et al (1963) that a midline lesion would have to elevate the anterior cerebral artery 1 cm to be outside the normal variation.

In addition to the value of a preoperative diagnosis angiography does by demonstrating the position of the anterior communicating artery give information which is of importance during operation (Olivecrona 19?)

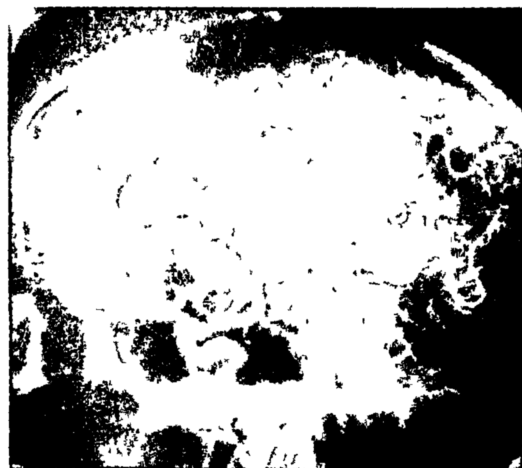


Fig. 1? Arteriography showing elevation of the anterior cerebral arteries and anterior communicating artery
a Lateral view



b Antero-posterior view (Case 30)

Pneumography

Angiography and pneumography are generally considered complementary procedures in the investigation of juxtachiasmatic tumours (Chase & Taveras 1961 El Banhawy & El Nadi 1962) Some investigators prefer angiography (Joy et al 1954 Tucker et al 1959 Bakay & Bean 1963), others pneumography (Schlezinger & Teplick *1948* Lindgren 1954 Walker 1962) Pneumolaminagraphy is a significant advance (Walker 1962, Samii et al 1968) According to El Banhawy & El Nadi *(1962)* encephalography gives a cross section of the tumour in the mid sagittal plane while angiography visualizes a cross section in the coronal plane at the level of the anterior cerebral arteries

Pneumographic evidence of a suprasellar tumour is a concave filling defect or obliteration of the chiasmatic and lamina terminalis cisterns (Davidoff & Epstein 1955) and a distorsion of the optic or infundibular recesses of the third ventricle Posterior displacement of the interventricular foramen and of the floor of the third ventricle or a defect in the floor of the anterior horn may occassionally be seen.

Quantitative data on the value of pneumography are even more scant than those on angiography. Table XII contains the available data. It appears that in our series the diagnosis was made in 8 of 11 cases ([illegible] %).

Judging from this, angiography seems slightly more effective in establishing the diagnosis but the use of [illegible]. In 3 of our cases (Nos. 5, 6 and 14) pneumography as well as angiography were negative. All 3 patients had small tumours. The same was observed by Jaffe & McKissock in 7 patients out of 17 with small tumours.

Isotope scanning

Walker (1962) found this method excellent for a general survey of a tumour suspected in the chiasmal region. [illegible] (196[illegible]) by means of 131 J labelled albumin demonstrated 3 of [illegible] parasellar [illegible] while Rasmussen et al. (1963) [illegible]. He found that parasellar [illegible] presumably because of their small size could not be detected. [illegible] et al. (1960) found scanning valuable in the diagnosis of suprasellar [illegible]. It was stressed that an accurate [illegible]

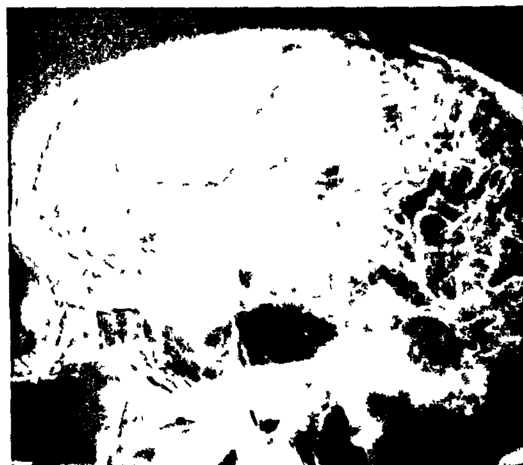


Fig. 13. Arteriography. Filling of tumour vessels in capillary phase. Plain radiography revealed no calcification in the tumour. (Case 7)

of 99 m Tc excludes chordomata and cholesteatomata and makes craniopharyngiomata and chiasma gliomata improbable Only pituitary adenomata should be able to give a similar concentration of activity In our series scanning procedures were not used It may be added that sphenoidal meningiomata can be demonstrated by 99 m Tc scanning (Heuer & Ehlers 1972)

TABLE XII

Value of contrast radiography in the diagnosis of suprasellar meningioma

Authors	Year	Total No of cases	Angiography			Pneumography			Angiography Pneumography		
			No.	Positive findings		No	Positive findings		No	Positive findings	
				No	%		No	%		No	
Davidoff & Epstein	1955	8	–			8	7	88	–		
Cassinari & Bernasconi	1957	35	15	15	100	–			–		
Passerini & Cecchini	1962	24	12	12	100	19	18	95	–		
Bakay & Bean	1963	9	9	9	100	9	9	100	9	9	100
Udvarhelyi et al.	1963	7	7	2	29	7	5	71	7	5	71
Lombardi	1967	34	17	17	100	–			–		
Jane & McKissock	1962	50				–			50	47	94
Small tumours		17	–			–			17	14	82
Large tumours		33	–			–			33	33	100
Present series	1973	31	25*	22	88	11	8	78	8	5	63
Small tumours		13	9	6	67	7	4	57	5	2	40
Large tumours		18	16	16	100	4	4	100	3	3	100

*) Case 13 with a sacculate aneurysm and case 20 with sphenoidal meningioma also gave positive findings but not of the suprasellar meningioma.

TREATMENT

The suprasellar meningioma is a histologically benign tumour. It grows slowly but threatens the patient through a gradual reduction of vision leading to blindness and finally to death by involving the hypothalamus.

The only radical treatment is surgical removal of the tumour as radiotherapy and chemotherapy are without effect. Operation should be performed as early as possible as removal of the smaller tumours is easier than the larger ones, and as the visual disturbances may aggravate rapidly, particularly when the tumour compresses the optic nerve at the optic foramen from below or grows into the optic canal.

According to Cushing the first to operate on a suprasellar meningioma was Krause in 1910. His patient had been observed since 19[illegible] because of failing vision and died shortly after the operation. The first report on satisfactory surgical treatment was published by Holmes & Sargent in 1927. In 9 of their cases the tumour was only partially removed; in the tenth case operated on by Sargent in 1927 the tumour was completely removed. However, as early as 1916 Cushing had removed such a tumour completely but he did not publish his cases until 1929. Since then a large number of papers dealing with diagnosis and surgical practice have been published as already mentioned.

Indication for operation

These are the logical consequences of what has been said about the natural history of the suprasellar meningioma. In all cases of gradually failing vision in one or both eyes, even just a central scotoma, a suprasellar meningioma should be considered the possible cause. If no other proper diagnosis is made, exploratory craniotomy is recommended.

Required examinations comprise careful ophthalmological examination, radiography of the skull, carotid angiography and pneumography. It must be emphasized that in the present series about one third of the patients had only unilateral symptoms and that even if radiological examinations are negative, suspicion should not be abandoned. This view is in accordance with those of Holub (1956) and Jane & McKissock (1962). The latter authors stressed that progressive visual failure or a field defect in one eye is enough to recommend exploration. It appears that little can be argued against operation. The risk is slight and non neoplastic lesions (mainly optochiasmatic arachnoiditis) are not accelerated by an operation (Jane & McKissock 1962, Horcajada & Salah 1970) but may rather improve (case 40266). As

Cushing & Eisenhardt put it In the case of impaired vision with bitemporal defects the safest rule is to look in and see what the cau e may be without delay

In the present series of 31 cases the pre operative diagnosis was one of suprasellar meningioma in 26 although in a few of these a craniopharyngioma or a pituitary adenoma was also considered as a possibility In 3 cases optochiasmatic arachnoiditis was considered most probable One case had a sphenoid ridge meningioma and in addition a small suprasellar meningioma which had caused no symptoms (case 20) Finally, in one case (No 13) the patient had observed failing vision for 2 years caused by a suprasellar meningioma which was however not found until the patient was operated on for an aneurysm which gave rise to paresis of the third cranial nerve

In the present series arteriography and pneumography were negative in 3 cases of small tumours Similar negative findings were reported by Jane & McKissock in 3 of 17 cases of small tumours (less than 3 cm in diameter) It is important in all cases to do arteriography and if necessary also pneumography in order to determine the size and extent of the tumour prior to operation and to exclude the possibility of an aneurysm

Technique of operation

In early attempts at surgical removal of suprasellar meningiomata a transnasal approach was used Sargent and Cushing both operated transfrontally Cushing extradurally dissecting the dura of the anterior fossa to the sphenoid ridge along which the dura was opened medially and the chiasmal region exposed Sargent and Dandy recommended a frontal transdural approach as in operation for pituitary adenoma and this method is to-day the most commonly used

In Handbuch der Neurochirurgie Olivecrona gave a detailed description of the technique of removing a suprasellar meningioma from which the technique used in the present series differs only slightly However as every surgeon works on the basis of his own experience differences will exist especially because the technique is continuously developing

To-day we recommend that operation on these patients as well as on those with pituitary adenomata should be performed under steroid cover The reason for this will be explained later The day before the operation the patient is given cortisone 200 mg and at the operation 200 mg The following days this dose is reduced by 25 mg daily

The first 7 patients in our series were operated on under local anaesthesia (1945 1950) the following patients with a single exception under general anaesthesia to day with slight hyperventilation

As regards the side from which the operation should be performed Olivecrona and Cushing recommended the right side in all cases which is technically easier for a right handed surgeon others (e g, Holub 1956 Grant & Hedges 1956) operated from the side with the severest visual loss Usually we also followed this rule but in some patients with a large tumour causing severe loss of vision in one eye and moderate impairment in the other, we operated on the least affected side as the purpose of the operation is to preserve the vision on this side Experience shows that on the side with severe loss of vision there is nearly nothing to gain by operation

At operation, a small craniotomy with a free bone flap is performed in the frontal region The dura is sewn up to the pericranium anteriorly and opened anteriorly

and along the base of the skull Usually, there is adequate space to reach the chiasmal region below the frontal lobe The arachnoid around the carotid artery is opened and after evacuation of cerebrospinal fluid there is sufficient space to expose the tumour Only in a few cases has it been necessary to puncture and drain the frontal horn or administer mannitol intravenously Olivecrona and Cushing recommended lumbar drainage to permit sufficient elevation of the frontal lobe if necessary supplemented with mannitol and hyperventilation McKissock recommended hypothermia and intravenous urevert

In most cases a small hemispherical tumour of reddish colour is found between the optic nerves and expanding on the floor of the anterior fossa The surface is slightly irregular covered by the arachnoid The optic nerves may be seen steeply elevated and distended as white bands The large tumours may extend far anteriorly sometimes even to the crista galli and the optic nerves may be pressed backwards and downwards In some cases a small round part of the tumour is extending beneath the optic nerve at the optic foramen elevating the distal part of the nerve which is spread out on the surface of the tumour and is pinched at the entrance of the optic canal Large tumours may partly cover or completely surround the optic nerve The anterior cerebral artery and the carotid artery may adhere to the tumour or may be surrounded by it In the latter circumstances Cushing considered the tumour inoperable

Only a few suprasellar en plaque meningiomata are reported (Learmonth et al 1931 Bucy & Kredel 1934 Meadows 1949 Guiot et al 1970) Olivecrona reported one case among his 64 suprasellar meningiomata In the present series two cases showed en plaque extensions from a globular tumour

The tumour receives its vascular supply from the dural attachment around the tuberculum sellae and further often receives small branches from the anterior cerebral artery When removing a small tumour we usually start cutting through its attachment by diathermy and excise the tumour in pieces In some cases it is possible when the attachment has been loosened to remove the tumour in one piece by blunt dissection from the surrounding structures Among 13 small tumours this was done in 8 cases (weight 2-6 g) Large tumours are excavated with a diathermy loop and going down to the attachment this is coagulated step by step At last the capsule is loosened from the surroundings great care being taken to avoid damage to the optic nerves chiasma and the anterior cerebral and carotid arteries If the anterior communicating is patent it is permissible to ligate one anterior cerebral artery but never two Olivecrona stressed the importance of preserving the small vessels from the anterior cerebral artery to the hypothalamus These vessels emerge from the anterior cerebral artery between the internal carotid and the anterior communicating so it is permissible to ligate the anterior cerebral at one of these places but never in both which would result in softening of the hypothalamus If the carotid artery is surrounded by the tumour both Olivecrona and Cushing found that it is not advisable to try to remove the tumour completely Olivecrona stated that a fatal outcome of operation for suprasellar meningioma is nearly always due to lesions of the carotid artery and of one or both anterior cerebral arteries

In one of our cases both anterior cerebral arteries and one carotid artery were damaged and fatal haemorrhage ensued (No 8) In 3 cases one anterior cerebral artery had to be ligated and in 2 cases haemorrhage from a carotid artery was stopped by muscle packing (Nos 8 and 21)

In four patients the tumour extended into the optic canal for approximately 1 cm The optic canal was opened and the tumour was removed Two of the patients had severe loss of vision, which did not improve (Nos 6 and 10) The third had moderate impairment and here the visual acuity improved and the visual field became normal (No 5) The fourth patient had no light perception in the left eye the tumour extended en plaque around the left optic nerve reaching the right optic nerve The tumour extended beneath the left optic nerve and 1 cm into the optic canal (No 29) Profuse bleeding from the ophthalmic artery ensued and could be controlled only by diathermy The nerve was infiltrated by the tumour and was resected up to the chiasma

In one patient (No 17 18) at re-operation the tumour was growing behind the infundibulum which was displaced forwards on the anterior aspect of the tumour The tumour was growing beneath both optic nerves the left eye was blind in the right the visual acuity was 0 4 Eight years earlier the patient had been operated on for a small meningioma attached to the tuberculum sellae When this was removed an excavation was seen between the optic nerves with the infundibulum in the concave bottom The new tumour was lying behind the infundibulum attached to the diaphragma and dorsum sellae reaching the edge of the tentorium but not involving the oculomotor nerve

Five patients showed hyperostosis in the presellar area at the operation In one case this was crater like with 1 cm high walls In all cases the attachment to the dura and hyperostosis were densely coagulated Only in a few cases was the tumour not radically removed

In one case (No 8) of a supposedly very large tumour a bifrontal craniotomy was made The tumour was exposed between the frontal lobes and through the anterior part of the corpus callosum A similar approach was used by Grant & Hedges (1956) in 4 cases In our case the patient died and the procedure cannot be recommended

COMPLICATIONS OF OPERATION

Postoperative deaths

Olivecrona stated that most fatal cases are caused by lesions of the large arteries Among his patients 14 died A postoperative haematoma was the cause of death in two meningitis in two and pulmonary embolism in one The remaining nine patients died from lesions of the carotid artery or one or both of the anterior cerebral arteries with softening of the hypothalamus In the series of Cassinari & Bernasconi (19.7) five of seven operative deaths were caused by haemorrhage

In our series 32 operations were performed in 30 patients Three cases of postoperative deaths occurred on the 7th 13th and 21st day respectively

In one of the patients (case 8) both anterior cerebral arteries had to be ligated Autopsy showed a perforated duodenal ulcer and death was probably caused by a hypothalamic lesion The two other patients who died probably also had lesions in the hypothalamus (cases 3 and 10) A case similar to No 10 (their case 1) was briefly reported by Holmes & Sargent (1927) The patient was a 30-year-old man who for 3 years had noticed failing vision and for 3 weeks had had headache and a few attacks of dizziness but no vomiting There were no clinical signs of pituitary insufficiency Vision in the right eye was so reduced that he could not count fingers with the left he read 6/36 The tumour was partially removed After a period of restlessness the patient died 13 days after the operation without any apparent cause Guillaume et al (19.7) mentioned that all 5 deaths in their series occurred under a picture of d(n.glement végetatif aigu grave

Case 8 43 year-old woman Failing vision for 3 years irregular menstruation for 2 years Large suprasellar meningioma Bifrontal craniotomy Severe haemorrhage ligation of both anterior cerebral arteries Postoperative unconsciousness Died on 7th postoperative day

A woman 43 years of age in 1951 who for 3-4 years had noted progressively failing vision especially in the right eye An ophthalmologist found visual acuity RE 0 05 LE 0 5 bilateral optic atrophy bitemporal hemianopia

On admission (Sept 1951) RE 0 1 LE 0.5 bilateral optic atrophy and regular bitemporal hemianopia Neurological examination normal sense of smell normal For 2 years the patient had had irregular menstruation Urinary excretion of hormones was normal X ray examination of the skull showed nothing abnormal reappraisal disclosed hyperostotic thickening of the sphenoidal planum and limbus Right carotid angiography revealed a very large suprasellar meningioma

Operation (Sept 1951 Malmros) Bilateral frontal craniotomy The frontal lobes were separated and the anterior part of the corpus callosum divided The tumour was exposed from

its superior aspect cavitated and removed in pieces The [illegible] surrounding structures and haemorrhage from the anterior cerebral arteries [illegible] only by ligation a haemorrhage from the right carotid artery by [illegible] The [illegible] ventricle was opened Tumour wight about 20 g Histological diagnosis [illegible] meningioma. After operation the patient was unconscious with high fever [illegible] up but on the 7th day an acute deterioration occurred and the patient died

Autopsy showed encephalomalacia of the basal parts of the frontal lobes and the [illegible] mus Coagulated blood in the third ventricle the aquaduct and in the [illegible] addition duodenal ulcers with acute perforation were disclosed

Case 10 37 year-old woman Decreasing vision during 3 years D [illegible] Removal of suprasellar meningioma Postoperative visual imp[illegible]ment D[illegible] operative day in hyperthermia

A 37 year-old woman (1953) who 3 years previously had experienced short period of dim vision in the left eye When similar symptoms appeared in the right eye in 1[illegible] the [illegible] noted that now her left eye was blind Two years prior to admission she had had an [illegible] because of failing vision with some transient improvement

On admission Visual acuity RE 0 33 LE no light perception Right disc normal left atrophic Perimetry showed a temporal hemianopia in the right eye A neurological examination showed nothing abnormal No endocrine dysfunctions X ray examination of the skull including the optic canals showed nothing abnormal Reappraisal disclosed hyperostosis limbus sphenoidalis. Bilateral carotid angiography showed curved elevation of the anterior cerebral arteries suggesting supra ellar meningioma.

Operation (Jan 1953 Malmros) Under local anaesthesia and through a left anterior craniotomy a tumour the size of a walnut was removed piecemeal The attachment to the dura was coagulated The left optic nerve which was infiltrated by the tumour was removed The tumour grew into the left optic foramen where profuse haemorrhage from the ophthalmic artery could be controlled only by coagulation The right anterior cerebral artery was ligated During the first few hours after operation the patient was awake and conscious then she became increasingly confused restless with a temperature running as high as 40 2° C (4th day) From 10th day normal temperature but she was still somewhat drowsy restless and unclean Visual acuity was RE 1 0 LE light perception Neurological examination normal

On the 11th day the patient was transferred to a local hospital where she died on the 21st day in hyperthermia. Postmortem examination no haemorrhage in the operative field No microscopic examinations performed

Table XIII shows the operative mortality in published series As regards the remarkably high mortality in some of these it should be noted that several of these tumours were apparently very large They should probably not have been classified as suprasellar Olivecrona regarded the junction of the falx with the posterior end of the crista galli as the anterior limit for a suprasellar meningioma According to Cushing tumours weighing more than 20 g are inoperable The significance of the tumour size appeared clearly from the series of McKissock Among 33 patients with large tumours (> 3 cm in diameter at the base) there were 4 postoperative deaths of 17 with small tumours no-one died

The present series comprises 13 small tumours (weight 2 6 g) 17 large tumours (weight 6-20 g) and one with a tumour weighing 40 g (case 4) Among the post operative deaths two cases had large tumours one a small tumour

Pituitary hypothalamic insufficiency

Diabetes insipidus is the postoperative complication most frequently mentioned in the literature In the present series this occurred in 3 patients in all cases it was only transitory The first case was a 45 year old woman with a 10 g tumour (case 16) the second a 47 year-old woman with a small tumour but where the infundibulum

TABLE XIII

Operative mortality and postoperative recurrence in suprasellar meningioma

Authors	Period	No of cases operated on	Postoperative deaths		Recurrence
			No	%	No
Holmes & Sargent	1912 27	10	2	20	–
Cushing & Eisenhardt	1916 37	24	3	13	2
Guillaumat	1931 36	22	8	36	–
Holub	1939 52	22	5	23	0
Cassinari & Bernasconi	1939-55	31	7	23	–
Grant & Hedges*)	1928 56	30	6	20	5 *)
Weber	65	44	17	38***)	1
Guillaume et al	1941 56	21	5	24	–
Olivecrona	1925 56	64	14	22	4
Jane & McKissock	1936-61	49	14	29	4
Small tumours		17	0	0	2
Large tumours		32	14	42	2
Present series	1945 71	31	3	10	2
Small tumours		13	1	8	2
Large tumours		18	2	11	0

*) The period is obtained from a maximal observation time of 28 years at the time of publication

**) All died from recurrence

***) Three more died from 1 week to 6 months after operation

had to be transected (case 18) the third a 51 year-old man who developed meningitis but was cured after 18 days (case 11) The two last mentioned patients had symptoms of permanent pituitary insufficiency and needed substitution therapy In addition permanent pituitary insufficiency occurred in a 61 year-old blind woman operated on for an 11 g tumour The condition was not recognized until after discharge (case 1) Finally a 72 year-old woman had severe symptoms with drowsiness fever and disturbed electrolyte regulation which all disappeared after steroid medication (case 21)

Case 21 72 year-old woman Failing vision in the right eye for 3 years in left for 1 year Discs pale Bitemporal hemianopia 10 g suprasellar meningioma 4 days after operation fever wound infection pneumonia Condition considered hopeless On steroid treatment quick restitution Died of cardiac failure 8 years later

A woman 72 years of age in 1963 previously in good health For 3 years decreasing vision in the right eye as shadows in the temporal visual field The last year also affection of the left eye

During the last year increasing body weight and a tendency to sweating especially in the night

On admission (May 1963) vision RE 0 1 LE 0 33 Bilateral optic atrophy and bitemporal hemianopia The patient was obese pale with a thin growth of hair

Neurological examination was normal X ray examination of the skull normal Right carotid angiography suggested a suprasellar tumour Biochemical examination revealed no pituitary insufficiency

Operation (May 1963 J H Rasmussen) Right frontal craniotomy A 10 g suprasellar meningioma was removed in toto and the attachment coagulated The tumour extended 4 cm in front of the sella and beneath the right optic nerve A lesion of the left carotid artery was controlled by muscle packing

Postoperative course The first 3 days after the operation were uneventful On the 4th da fever developed and the patient became delirious and restless because of a mening al infection The cerebrospinal fluid was haemorrhagic pressure 300 mm H_2O The general condition deteriorated in spite of antibiotic treatment Serum electrolytes were normal and steroid treatment was not considered indicated On the 20th postoperative day signs of pneumonia Serum sodium showed a decreasing tendency and the patient was oedematous

The condition was considered hopeless and steroid treatment (cortisone) was started On this treatment the patient cleared up and after 3 weeks she was fully restituted Eye exami nation showed visual acuity RE 0 33 LE counting of fingers atrophic discs Bitemporal hemianopia. The patient was transferred to a local hospital she was given cortisone 12 5 mg x 3 and thyreoidine

Follow up After 5 months the patient was in good health No sweating tendency Vision RE 0 25 LE 0 05 Optic atrophy and bitemporal hemianopia. After 1 year vision in RE 0 33 LE 0 1 Ophthalmoscopy and perimetry unchanged Her hypopituitarism was well compen sated

She died 8 years after the operation (80 years old) from cardiac failure No autopsy

On the basis of our clinical experience we find it indicated to perform operation on patients with suprasellar meningiomata under steroid cover Lundberg & Hugosson (1966) showed that even if clinical symptoms of pituitary insufficiency may not be present the metopirone test may be positive in patients with suprasellar meningio mata because the tumour interferes with the anterior part of the hypothalamus Olivecrona stressed the risk of injury to the small arterial branches which run from the first part of the anterior cerebral artery to the hypothalamus Even in cases in which the anterior cerebral artery has not been ligated it cannot be excluded that these vessels are damaged by the dissection in the chiasmal region resulting in hypothalamic insufficiency

Other complications

A haematoma in the frontal lobe occurred in the immediate postoperative period in a 62 year-old woman (case 26) with arterial hypertension In this patient and a 72 year-old woman (case 30) wound infection developed The bone flap was removed and later replaced by an acrylic plate In the period when local anaesthesia was used a patient became unconscious for a short period when it was attempted to loosen a retrochiasmal part of the tumour (case 7) so this part of the tumour was left In another patient operated on under general anaesthesia extrasystoles and later atrial fibrillation developed when the retrochiasmal part of the tumour was drawn on This danger in operating retrochiasmal tumours was also mentioned by Guiot et al (1970) Neither before nor after the operation did these patients reveal any signs of cardiac disease

Anosmia was noted postoperatively in 3 cases (Nos 7 24 and 28) Epilepsy de veloped in 2 patients They were subjected to operation at the age of 43 and 55 and seizures occurred after 7 and 1 year respectively (cases 15 and 28) As regards complications of long duration Olivecrona mentioned that among 50 patients two had epilepsy two diabetes insipidus two hemiplegia and two postoperative arach noiditis with decreasing vision

RESULTS

Immediate visual results

Table III summarizes the ophthalmological findings in the present series immediately after operation i.e. before discharge of the patient. As regards effective visual acuity 12 patients were improved, 12 unchanged and 7 worse (Table IV). The average effective visual acuity before operation was 76 %, after operation it was 77 %. As far as the visual field score was concerned, 14 cases were improved, 9 unchanged and 7 worse. The average field score before operation was 47 %, after operation it was 57 %.

It has been stated (Cushing, Olivecrona, Grant & Hedges) that in case of severe visual loss postoperative improvement is rare, the change rather being a further deterioration. Severe postoperative visual deterioration was seen in 7 patients in the present series.

A 61 year-old woman (case 1) who before operation had a visual acuity of 0.05 in the right eye and light perception in the left and bitemporal hemianopia was completely blind after operation. A 58 year-old woman (case 7) with pre-operative normal vision in the right eye and 0.1 in the left had after the operation 0.25 in the right and no light perception in the left. A 51 year-old man (case 11) with pre-operative vision reduced to counting of fingers in the right eye and 0.67 in the left was postoperatively blind in the right eye but had normal vision in the left. A 45 year old woman (case 16) with pre-operative vision of 0.67 in both eyes could after the operation only count fingers in the right while the visual acuity in the left was 0.5. A 72 year-old woman (case 21) had before the operation a vision of 0.1 in the right and 0.33 in the left eye. After operation visual acuity in the right eye had increased to 0.33 while in the left it was only finger counting. A 63 year-old man (case 22) with finger counting and 0.33 before the operation had afterwards only vision 0.05 in the right eye and 0.15 in the left eye. Finally a 61 year old woman with recurrence of tumour after 22 years and pre-operative severe visual reduction in the left eye was blind in this eye after the operation (case 5). Udvarhelyi & Walsh (1962) discussed in detail the various causes of postoperative visual deterioration in patients operated on in the chiasmal region.

Late results

Only a few series are available from which the long term visual prognosis appears. In the series of Cushing 13 patients were re-examined 5 to 21 years after operation

Vision was good in 10 and poor in 3 Jane & McKissock (1962) reported on a series operated on during the period 1936–61 of 18 patients with large tumours 8 showed improvement, 6 were unchanged, while 4 had reduced vision The exact time of observation was not stated Among 17 patients with small tumours vision was improved in 9 and unchanged in 8 Olivecrona (1967) stated that the results with regard to vision depend mainly upon the condition of the eyes before operation There were 5 patients with only moderate impairment of vision In all of these normal vision and normal fields were restored, although in one case only partial removal had been possible In 25 cases visual acuity was below 2/60 in one eye and moderately impaired in the other In 12 cases vision remained unchanged 9 regained useful vision in the best eye and 4 showed marked improvement in both eyes Visual acuity was below 2/60 in both eyes in 4 patients and this condition persisted after removal of the tumour In 6 patients one eye was blind and the other moderately affected The condition remained unchanged in 2 patients while four regained useful vision in the best eye In 4 cases one eye was blind while the other was normal the condition remained unchanged in all of them The result was the same in 5 patients who were blind in one eye and vision reduced to light perception in the other

In the present series, 24 cases could be followed up after an average period of 7 7 years (Tables III, IV and XIV) It appears from these tables that the vision obtained at operation was maintained The analysis presented in Table XIV suggests that the age or sex of the patients does not exert any influence upon the immediate and late visual results as evaluated from visual acuity and visual fields

TABLE XIV

Influence of age, sex, tumour size and histopathology on the visual prognosis

	Immediate visual results				Late visual results			
	No	Improved	Unchanged	Deteriorated	No	Improved	Unchanged	Deteriorated
Total	29	14	10	5	22	10	8	4
< 40	11	5	5	1	7	2	4	1
40–60	14	7	4	3	11	6	3	2
> 60	4	2	1	1	4	2	1	1
Women	23	12	7	4	17	8	6	3
Men	6	2	3	1	5	2	2	1
Large	17	7	6	4	12	5	5	2
Small	12	7	4	1	10	5	3	2
E	12	4	5	3	8	3	4	1
E + F	11	7	3	1	10	6	2	2
F	6	3	2	1	4	1	2	1

The „visual results were estimated on the basis of visual acuity and visual field Full data are given in Tables III and IV Late visual results comprise 22 cases in whom follow up examinations were performed after an average period of 7 7 years (range 1 to 24 years)

Case 20 was excluded as it was asymptomatic In the late results case 7 was also excluded

The immediate results for the small tumours appear to be slightly better than those for the large ones, but at the follow up examination no difference was observed As regards the histopathological classification Table XIV might suggest that the endotheliomatous meningioma has a graver prognosis than the other types, but the differences are not statistically significant and at the follow up examination no differences were found

Survival

Apart from the still rather high operative mortality rate (Table XIII) the patients rarely die from their suprasellar meningioma However, specific information about this is sparse In the series of Cushing 7 patients died from 6 weeks to 11 years after operation while 13 patients could be re examined 5 to 21 years after operation

In the present series no patients died from their tumour 17 patients were alive after an average period of 8 7 years (1 to 24 years) 8 patients had died after an average of 11 5 years Of these 2 died after only 1 year The first (case 6) died in a local hospital Diagnosis was pneumonia No autopsy was made The second case (No 20) had multiple lesions a suprasellar a sphenoidal and two convexity meningiomata He died in a local hospital Diagnosis was arteriosclerosis No autopsy was made

Recurrence

The incidence of recurrence appears to be low in all series of suprasellar meningioma (Table XIII) Among 20 patients Cushing & Eisenhardt observed 2 cases of recurrence (Nos 5 and 20) The first died 10 years after operation with sign of recurrence The second was subjected to re-operation after two years following which there was no recurrence during the next 10 years Simpson (1957) who reported recurrence in 21 % of a series of 322 intracranial meningiomata found no recurrences among the 21 suprasellar meningiomata included Jane & McKissock (1962) observed recurrence in 12 % of their patients with large tumours Olivecrona reported recurrence in 4 out of 17 cases after partial removal After complete extirpation (47 cases) no recurrence was observed during an observation period ranging from 1 to 29 years Three of the recurrent cases were subjected to re-operation with satisfactory improvement of vision In the fourth case no operation was indicated as the visual condition was unchanged and the only complaint was a slight headache

In the present series recurrence was seen in two patients A 75 year-old woman (case 12) had severe unilateral visual impairment 16 years after the operation At operation a small hyperostosis had been observed and the tumour was supposed to be completely removed Now the other eye was normal and re-operation was not done The second patient was a 61 year-old woman (case 5) who 22 years after operation experienced severe visual loss in one eye and moderate visual loss in the other A large recurrent tumour was removed Vision was totally lost in the best eye because the tumour had grown beneath the optic nerve and into the optic foramen In a third patient (case 17 18) with visual disturbances several years after the first operation a new tumour was found behind the infundibulum

It may be concluded that although recurrences are rare, they may be encountered even decades after the operation It is recommended that patients operated on for suprasellar meningiomata are kept under ophthalmological control for the rest of their lives

CONCLUSIONS AND SUMMARY

A suprasellar meningioma is defined as a tumour arising from the presellar area in front of and around the tuberculum sellae and growing upwards between the two optic nerves The classical syndrome consists of bitemporal visual field defects with optic atrophy and a normal sella turcica in an otherwise healthy person

The present survey is based on an analysis of a series of 31 cases operated on at Århus Kommunehospital in the period 1943–1971 For comparison a review of the literature has been undertaken

The initial subjective symptom is monosymptomatic failing vision found in about 75 per cent of the patients At first only one eye is affected Larger visual field defects may not be present at this stage but careful perimetry is likely to disclose a central scotoma The observed reduction of the visual acuity may be of any degree blindness in one eye and normal vision in the other being a rather common finding

In more advanced stages visual field defects of a bitemporal nature occur They are more irregular and asymmetrical than in patients with pituitary adenoma A specific type or a characteristic development apparently does not exist Optic disc atrophy is also a relatively late sign while papilloedema is extremely rare and late occuring only as a result of increased intracranial pressure

More uncommon presenting symptoms are visual field constrictions periocular pain diplopia and possibly visual hallucinations Symptoms and signs other than ophthalmological are rare Headache is not typical anosmia occurs only with very large tumours Neurological examination is, as a rule normal

The suprasellar meningioma is more frequent in women than in men, the ratio being about 3 to 1 As in the pituitary adenoma and the craniopharyngioma the symptomatology is influenced by pregnancy but the mechanism is still obscure The suprasellar meningioma may occur in the adult at any age most patients being between 35 and 45 years of age

The present analysis revealed no significant influence of age, sex tumour size or histopathology upon the pre operative history, although the figures suggest that optic atrophy is more common in older patients, and that the disease runs a shorter course in men who are affected at a slightly higher age

The differential diagnosis is discussed in two groups 1) the patients with mono symptomatic failing vision and 2) the chiasmal syndrome The positive diagnosis of a suprasellar meningioma is based on the exclusively ophthalmological history

van Bogaert L (1929) Le diagnostic des tumeurs suprasellaires et en particulier des tumeur de la poche pharyngienne de Rathke
13 Concilium ophthal Hollandia III 1 61

van Bogaert L (1929) Erreurs de diagnostic pseudoparalysie générale avec atrophie optique primaire Autopsie méningiome suprasellaire
J Neurol Psychiat 29 229 233

Bollack J Da id M & Fuch I (1937) Les arachnoidites optochiasmatiques étude ophtalmologique et neuro-chirurgicale
Soc franç Ophtal Masson Paris

Bonamour G B net M & Laffay (1971) Contribution a l'etude du syndrome chiasmatique survenant au cours de la grossesse
Ann oculist. Paris 204 35 56

Borel G (1929) Diagnostic précoce des tumeurs et affections suprasellaires et leur vérification anatomique d 8 a 37 ans plus tard
13 Concilium ophthal Hollandia III 6 0 681

Boselli F & Jefferson A A (1957) Electroencephalogram with chromophobe adenomata and Rathke pouch cyst Modification by associated metabolic disorder
EEG u Cl Neurophysiol 7 0

Brouwer B 1929 Some remarks on differences in the visual field of the intra and suprasellar tumours
13 Concilium ophthal Holland a III 6 4 76

Bucy P C & Kredel F F (1934) Meningioma of the tuberculum sellae with hyperostosis
Amer J Pathol 10 605-620

Busch F & Mahneke A 1 1 A case of meningioma from the diaphragm of the sella turcica.
ZH Neurochir 11 8

Cairns H (1933) Peripheral ocular palsies from the neuro-surgical point of view
Trans ophthal Soc U K 53 4 1 482

Cassinari V & Bernasconi V (1957) Considerazioni clinico-radiologiche su 35 casi di meningioma del tuberculo della sella
Acta Neurol Napoli 12 615 66

Chambers B M (1950) Meningioma of the tuberculum sellae
Amer J Ophthal 33 1417 1418

Chase N F & Taveras J M (1961) Cerebral angiography in the diagnosis of suprasellar tumors
Amer J Roentgenol 86 154 165

Christiansen V (1927) Les syndromes simples de la region chiasmatique
Bruxelles-médical 7 1246-1259

Christiansen V (1929) Difficultés de diagnostic differentiel des tumeurs supra-sellaires
13 Concilium ophthal Hollandia III 81 95

Cophignon J Djindjian R Caron J P & Houdart R (1969) Etude angiographique de la vascularisation des tumeurs hypophysaires
Neuro-Chirurgie Paris 15 439-450

Coulonjou R le Bo ec E & Salaun A (1950) Une erreur de diagnostic instructive méningioma supra sellaire pris pour arachnoidite opto-chiasmatique
Rev Oto-Neuro-Ophtal 563 571

Cushing H (1922) The meningiomas (dural endotheliomas) Their source and favoured seats of origin.
Brain 45 282 316

Cushing H (1929) The chiasmal syndrome of primary optic atrophy and bitemporal field defects in adult patients with a normal sella turcica
13 Concilium ophthal Hollandia III 97 184

Cushing H (1930) The chiasmal syndrome of primary optic atrophy and bitemporal field defects in adults with a normal sella turcica.
Arch Ophthal Chicago 3 505 551, 704 735

Cushing H & Eisenhardt L (1929) Meningiomas arising from the tuberculum sellae With the syndrome of primary optic atrophy and bitemporal field defects combined with a normal sella turcica in a middle aged person
Arch Ophthal Chicago 1 1-41 168 206

Cushing H & Eisenhardt L (1938) Meningiomas their classification regional behaviour life history and surgical end results Thomas Springfield USA

Dandy W E (1922) Prechiasmal intracranial tumors of the optic nerves
Amer J Ophthal 5 169 188

David M & Hartmann E (1935) Les symptoms dans les méningiomes de la petite aile du sphenoide
Ann oculist Paris 172 177 212

Davidoff L M & Epstein B S (1955) The abnormal pneumoencephalogram
Lea & Febiger Philedelphia p 157 162

Davis L (1931) Chiasmal symptoms in intracranial tumors ✓
Arch. Ophthal Chicago 6 181 212

Dawson B H (1958) The blood vessels of the human optic chiasma and their relation to those of the hypophysis and hypothalamus
Brain 81 207 217

Dechaume J P Wertheimer P & Milleret P (1949) Réflexions sur une statistique de 114 meningiomes intracraniens
Rev Neurol 81 321 331

DiChiro G & Lindgren E (1952) Bone changes in cases of suprasellar meningioma
Acta radiol Stockholm 38 133 138

Dollfus M A Puech & Guillaumat L (1937) Méningiome supra sellaire volumineux et calcifie chez un homme de 67 ans Conduite à tenir
Bull Soc Ophtal Paris 49 195-197

Driesen W & Schmidt H (1959) Intra und suprasellare Tumoren im Angiogram der Arteria carotis
Acta Neurochir 7 461 476

El Banhawy A & El Nadi F (1962) Carotid angiography in diagnosis of sellar and supra sellar space occupying lesions
J Neurosurg 19 495 504

Elkington S G (1968) Pituitary adenoma Preoperative symptomatology in a series of 260 patients ✓
Brit. J Ophthal 52 322 328

Elkington S G & McKissock W (1967) Pituitary adenoma Results of combined surgical and radiotherapeutic treatment of 260 patients
Brit. med J 1 263 266

Enoksson P (1965) Perimetry in neuro-ophthalmological diagnosis ✓
Acta ophthal Kbh suppl 82 pp 54

Enoksson P Lundberg N Sjostedt S & Skanse B (1961) Influence of pregnancy on visual fields in suprasellar tumours
Acta neurol scand 36 524 538

Espinosa M G (1946) Ueber nicht hypophysare Chiasmasyndrome
Bibl ophthal Fasc. 32 pp 1 60 Karger Basel

Esterman B (1967) Grid for scoring visual fields I Tangent screen
Arch Ophthal Chicago 77 780 786

Esterman B (1968) Grid for scoring visual fields II Perimeter
Arch Ophthal Chicago 79 400-406

Farnier G & Sedan R (1969) Cholestéatome supra sellaire Confrontation ophtalmologique et neuro-chirurgicale
Arch Ophtal Paris 29 491-496

Favory A (1926) Le syndrome chiasmatique Doin Paris

Favory A (1926) Les syndromes chiasmatique d origine syphilitique
Arch Ophtal Paris 43 203 226

Feiring E H & Shapiro J H (1964) Evaluation of angiography in the diagnosis of supra sellar tumors
Amer J Roentgenol Rad Therapy and Nucl Med 92 811 828

Fischer F (1931) Schwangerschaftsveranderungen der Hypophyse als Ursache bitemporaler Hemianopsie
Zschr f Augenheilk 75 343 354

Fischer F (1935) Über die Ursachen bitemporales Hemianopsie bei Schwangerschaft
Zschr f Augenheilk 85 88 108

Fledelius H (1970) Ultrasound (A mode) in a case of nasal posterior scleral ectasy
Acta ophthal Kbh 48 502 507

Fortier H W & Bouwarth W F (1967) Meningioma of the tuberculum sellae as a cause of optic atrophy
Amer J Ophthal 64 908 910

François J Neetens A & Collette J M (1956) Vascularization of the optic pathway No V Chiasma
Brit J Ophthal 40 730 741

Glaser J S Hoyt W F & Corbett J (1971) Visual morbidity with chiasmal glioma Long term studies of visual fields in untreated and irradiated cases
Arch Ophthal Chicago 85 3 12

Glees M (1956) Über die lokalisatorische Bedeutung der zentralen und parazentralen Skotome
Ber dtsch ophthal Ges 59 40 46

Glees M & Zielinski H (1956) Über bitemporale zentrale und parazentrale Skotome bei verschiedenen krankhaften Prozessen im Sellabereich
Klin Mbl Augenheilk 129 145 160

Globus J H (1933) Tumors affecting the optic chiasm and optic tracts
Arch Ophthal Chicago 9 729 750

Godtfredsen Erik (1944) Ophthalmologic and neurologic symptoms at malignant nasopharyngeal tumours
Acta ophthal Kbh suppl 22 pp 323

Goutelle A Allègre G E Lapras C Dechaume J P & Pacon R (1970) Méningiomes supra sellaires anterieurs
Neuro-Chirurgie 16 359 366

Grant F C & Hedges T R (1956) Ocular findings in meningiomas of the tuberculum sellae
Arch Ophthal Chicago 56 163 170

Grote W (1964) Zur Klinik und Behandlung der Tumoren des Nervus opticus und des Chiasmas
Klin Mbl Augenheilk 144 841-855

Guillaumat L G J (1937) Les méningiomes supra sellaires
These Picavet Boulogne Paris

Guillaume J Billet R Caron J P & Cuccia D (1957) Les meningiomes Etude clinique et chirurgicale
Presse universitaires de France Paris pp 107 115

Guiot G Montrieul B Goutelle A Comoy J & Langie S (1970) Meningiomes supra sellaires retro-chiasmatiques
Neuro-Chirurgie 16 273 285

Guttmann E & Spat H (1929) Die Meningiome des vorderen Chiasmawinkels eine gut charakterisierte Gruppe der Meningiome
Nervenarzt 2 581 591

Hagedoorn A (1937) The chiasmal syndrome and retrobulbar neuritis in pregnancy
Amer J Ophthal 20 690-699

Hamby W B (1952) Intracranial aneurysms
Charles C Thomas Springfield

Hardy J & Robert F (1969) Un meningiome de la selle turcique Variete sous-diaphragmatique. Exérese par voir transsphénoidale
Neuro-Chirurgie Paris 15 535 543

Hartmann E (1945) Optochiasmic arachnoiditis
Arch. Ophthal Chicago 33 68 77

Hartmann E & Guillaumat L (1937) Symtomes oculaires des meningiomes supra sellaires
Ann oculist Paris 174 1 39

Heinrichsdorff P (1914) Ein Psammom im vorderen Chiasmawinkel
Klin Mbl Augenheilk 53 185 187

Henderson W R (1938) The anterior basal meningiomas
Brit J Surg 26 124 165

Heuer H E & Ehlers N (1972) L orbitographie avec le technetium 99 m dans le diagnostic des tumeurs orbitaires
Ann oculist Paris 205 283 290

Hierons R & Lyle T K (1959) Bilateral retrobulbar optic neuritis
Brain 82 56 67

Hilton G F & Hoyt W F (1966) An arteriosclerotic chiasmal syndrome Bitemporal hemianopsia associated with fusiform dilatation of the anterior cerebral arteries
J amer med Ass 196 1018 1021

van der Hoeve J (1940) Diagnostic des tumeurs de la region supra sellaire
Ophthalmologica 99 258-264

Holmes G (1929) Suprasellar tumours
13 concilium ophthal Hollandia III 65 79

Holmes G & Sargent P (1927) Suprasellar endotheliomata
Brain 50 518-536

Holub K (1956) Intrakranielle Meningeome
Acta neurochir 4 355-401

Horcajada J & Salah S (1970) Ist der bitemporale Ges chtsfeldausfall an sich eine Indikation zur Chiasmarevision?
Wien klin Wschr 120 852 854

Horrax H (1939) Meningiomas of the brain
Arch Neurol Psychiat 41 140 157

Huber A (1956) Augensymptome bei Hirntumoren
Verlag Hans Huber Bern

Hughes B (1962) Indirect injury of the optic nerves and chiasma
Bull Johns Hopk Hosp 111 98 126

Hugonnier M R Didier Laurent A Modrin D & Magnard G (1968) Syndrome de névrite optique au cours des méningiomes du tubercule de la selle A propos de deux observations
Bull Soc Ophtal France 68 678 681

Jacquemin P J & Trippiat M (1969) Les arachnoidites optochiasmatiques
Bull Soc belge Ophtal 152 550 594

Jane J A & McKissock W (1962) Importance of failing vision in early diagnosis of supra sellar meningiomas
Brit med J 2 5 7

Jefferson G (1937) Compression of the chiasma optic nerves and optic tracts by intracranial aneurysms
Brain 60 444 487

Jefferson G (1945) On compression and invasion of the optic nerves and chiasma by neighbouring gliomas
Trans ophthal Soc U K 65 262 304

Joy H H (1952) Suprasellar meningioma Report of an atypical case
Amer J Ophthal 35 1139 1146

Joy H H Ecker A & Reimenschneider P A (1954) The role of cerebral angiography in ophthalmology
Amer J Ophthal 37 55 68

Kearns T P & Wagener H P (1953) Ophthalmologic diagnosis of meningiomas of the sphenoidal ridge
Amer J med Sci 226 221 228

Kelly R (1963) Lesions of the optic chiasm due to compression
Trans ophthal Soc U K 82 149 164

Laursen A Bruun (1971) Traumatic bitemporal hemianopsia
Acta ophthal Kbh 49 134 142

Learmonth J R Lillie W I & Kernohan J W (1931) Unusual surgical lesions affecting the optic nerves and chiasm
Amer J Ophthal 14 738 749

Ley A (1970) Meningiomas del „tuberculum sellae
Arch Soc Oftal Hisp Amer 30 241 270

Lindgren E (1954) Rontgenologie Handb der Neurochirurgie Springer Berlin

Lisserato S & Cosmettatos G F (1916) Sui tumori della regione ipotalamica del cervello intermedio
La riforma medica 32 449-461

Logan W C & Gordon D S (1967) Traumatic lesions of the optic chiasma
Brit. J Ophthal 51 258 260

Lombardi G (1967) Radiology in Neuro-Ophthalmology
Williams & Wilkins Comp Baltimore

Lorentzen S F (1966) Drusen of the optic disk
Acta ophthal Kbh suppl 90 pp 180

Lundberg P O & Hugosson P (1966) Application of the metopirone test to tumours in the region of the sella turcica
J Neurosurg 25 543 548

Lyle T K & Clover P (1961) Ocular symptoms and signs in pituitary tumours
Proc roy Soc Med 54 611 619

Manolesco D & Schmitzer G (1934) Contribution a l étude des tumeurs de la région sellaire
Rev Oto-Neuro-Ophtal 12 661 671

de Martel T Monbrun & Guillaume J (1931) L avenir ophtalmologique des operes de tumeurs de la région hypophysaire
Arch. Ophtal Paris 48 529 540

Marx E & Boevé H J (1932) Meningiomes de la selle turcique
Arch Ophtal Paris 49 417-426

Matheuson W R (1946) Meningioma of the tuberculum sellae with bi temporal hemianopia
Brit J Ophthal 30 9? 10?

Meadows S P (1949) Optic nerve compression and its differential diagnosis
Proc roy Soc Med 42 1017 1037

Meyer H J (1965) Das Chiasma Trauma
Klin. Mbl Augenheilk 146 833-845

Migliavacca F & Cassinari V (1955) Tumori cerebrali e gravidanza
Chirurgia 10 10 quoted by Passerini & Cecchini

Mooney A J & McConnell A A (1949) Visual scotomata with intracranial lesions affecting the optic nerve
J Neurol Neurosurg Psychiat 12 205 218

Nachtigaller H & Hoyt W F (1970) Storungen des Seheindruckes bei bitemporaler Hemi anopsie und Verschiebung der Sehachsen
Klin. Mbl Augenheilk 156 821-836

Newell F W & Beaman T C (1958) Ocular signs of meningioma
Amer J Ophthal 45 30-40

Olivecrona H (1927) Die chirurgische Behandlung der Gehirntumoren Springer Verlag Berlin pp 106 108

Olivecrona H (1938) Über die Bedeutung der Augensymptome für die topische Diagnose der Hirntumoren
Acta ophthal Kbh 16 431-445

Olivecrona H (1967) The suprasellar meningiomas Handb der Neurochirurgie Bd 4 III pp 167 172

Passerini A & Cecchini A (1962) I meningiomi del tuberculo sellare (studio radiologico di 24 casi)
Nunt. Radiol 10 82? 841

Philippides D Montrieul B & Levy R (1953) A propos de trios cas de meningiome du tubercule de la selle
Rev Oto-neuro-ophtal 25 16 22

Planiol T & Betti O (1961) Diagnostic des meningiomes intracraniens par la gamma-en cephalographie
Rev Neurol 105 420-429

Pommier M L (1970) Syndrome chiasmatique et grossesse
Bull Soc. franç Ophtal 70 272 275

Puech P & Mahoudeau D (1935) Les arachnoidites opto-chiasmatiques Leur diagnostic et les indications therapeutiques
Gaz med de France 3 101 109

Rasmussen P Buhl J Busch H Haase J & Harmsen A (1970) Brain scanning cerebral scintigraphy
Nord Med 84 1134 1139

Riise D (1966) Visual field defects in optic disc malformation with ectasia of the fundus
Acta ophthal Kbh 44 906 918

Riise D (1970) Neuro-ophthalmological patients with bitemporal hemianopsia
Acta ophthal Kbh. 48 685-690

Rintelen F (1969) Gesichtsfelddefekte bei Hirntumoren
Ophthalmologica 158 451-468

Rubin P & Kramer S (1965) Ectopic pinealoma A radiocurable neuroendocrinologic entity
Radiology 85 512 523

Rucker C W & Kearns T P (1961) Mistaken diagnoses in some cases of meningioma
Amer J Ophthal 51 15 19

Ruggiero G (1957) L encéphalographie fractionnée
Masson Paris pp 349 353

Russell D & Rubinstein I J (1971) Pathology of tumours of the nervous system
Arnold London pp 48 64

Rønne H (1938) The focal diagnostic of the visual path
Acta ophthal Kbh 16 446 543

Samii M Jork K & Schurmann K (1968) Die Pneumoenzephalo-Tomographie in der Differentialdiagnostik tumoröser und entzündlicher sellanaher Prozesse
Klin Mbl Augenheilk 153 761 770

Sargent P (1924) Some points in the surgery of the pituitary gland
Brit J Surg 11 521 532

Scatliff J H & Bull J W D (1965) The radiological manifestations of suprasellar metastatic tissue
Clin Radiol 16 66 70

Schaeffer J P (1924) Some points in the regional anatomy of the optic pathway
Anat Rec. 28 243 279

Schlernitzauer D A Hodges F J & Bagan M (1971) Tuberculoma of the left optic nerve and chiasm
Arch Ophthal Chicago 85 75 78

Schlesinger N S Alpers B J & Weiss B P (1946) Suprasellar meningiomas associated with scotomatous field defects
Arch Ophthal Chicago 35 621 642

Schlesinger N S & Teplick J G (1948) The diagnosis of suprasellar tumors by pneumoencephalography
Amer J Roentgenol and Radium Therapy 60 213 218

de Schweinitz G E (1923) Concerning certain ocular aspects of pituitary body disorders mainly exclusive of the usual central and peripheral hemianopic defects
Trans ophthal Soc U K 43 12 109

Simpson D (1957) The recurrence of intracranial meningiomas after surgical treatment
J Neurol Neurosurg Psychiat 20 22 39

Simson L R Lampe I & Abell M R (1968) Suprasellar germinomas
Cancer 22 533 544

Smith R J S (1965) Visual fields in suprasellar lesions
Trans ophthal Soc U K 84 697 711

Stern W E (1950) The lumbar cerebrospinal fluid protein in intracranial meningiomas
Brain 73 72-83

Stewart J (1899) The symptomatology of tumors involving the hypophysis cerebri
Trans Ass amer Phys 14 282 289

Sunderland S (1948) Neuovascular relations and anomalies at the base of the brain
J Neurol Neurosurg Psychiat 11 243 257

Towne E B (1934) A small meningioma arising from the tuberculum sellae
Arch Neurol Psychiat. 32 802 803

Tucker R L Holman C B McCarty C S & Dockerty M B (1959) The roentgenologic manifestations of meningiomas in the region of the tuberculum sellae
Radiology 72 348 355

Turner J W A (1943) Indirect injuries of the optic nerve
Brain 66 140 151

Tonnis W Steinmann H W & Krenkel W (1953) Electroencephalographische B fur de bei 44 Tumoren der Sellagegend
Acta Neuroveg 5 291 305

Udvarhelyi G B Langfitt T W & Cox A (1963) Neuroradiologic diagnostic procedures in suprasellar space-occupying lesions with special reference to angiographic measuremen s
Acta radiol 1 485 508

Udvarhelyi G B & Walch F B (1962) Complications involving the optic nerves and chiasm during the early period after neurosurgical operations
J Neurosurg 19 51 64

Uihlein A & Rucker C W (1958) The neurosurgeon s role in acute visual failure
Arch Ophthal Chicago 60 223 229

Uihlein A & Weyand R D (1953) Meningiomas of anterior clinoid process as a cause of unilateral loss of vision
Arch Ophthal Chicago 49 261 270

Vail D (1938) Optochiasmatic arachnoiditis importance of a m xed type of atrophy of the optic nerve as a diagnostic sign
Arch Ophthal Chicago 20 384 394

Velter E (1936) Le diagnostic des affections de la region chiasmatique et sellaire
Arch Ophtal Paris 53 593 615

Vérin P (1963) Pronostic vital et fonctionnel des meningiomes supra sellaires
These Universite de Bordeaux pp 317

Vesterdal E (1969) Accident insurance problems in ocular injuries
Acta ophthal Kbh 47 276-278

Walker A E (1962) The neurosurgical evaluation of the chiasmal syndromes
Amer J Ophthal 54 563 581

Walsh F B (1957) Clinical Neuro-Ophthalmology
Williams & Wilkins Baltimore

Walsh F B Chambers J W & Lloyd L A (1956) The ocular signs of tumours involving the anterior visual pathways
Amer J Ophthal 42 347 377

Walsh F B & Gass J D (1960) Concerning the optic chiasm Selected pathologic involve ment and clinical problems
Amer J Ophthal 50 1031 1047

Weber G (1965) Symptomatologie und Chirurgie der ellaren und suprasellaren Tumoren
Ophthalmologica 149 326 342

Westby R K (1963) Central paracentral scotoma and intracranial tumour
Acta ophthal Kbh 41 749 756

Weyand R D McCarty C S & Wilson R B (1951) The effect of pregnancy on intra cranial meningiomas occurring about the optic chiasm
Surg clin North Amer Mayo Clin Number Saunders Philadelphia pp 1225 1233

Wickbom I (1948) Angiography of the carotid artery A study of its value in the tumour diagnosis especially in comparison with pneumography
Acta radiol suppl 72 pp 90

Williamson Noble F A (1939) The ocular consequences of certain chiasmal lesions
Trans ophthal Soc U K 59 627 682

Østerberg G (1938) Traumatic bitemporal hemianopia (sagital tearing of the optic chiasma)
Acta ophthal 16 466-474

SUBJECT INDEX

Age 11 36 61
Aneurisms differential diagnosis 42
Angiography 47
Anosmia 26
Anterior cerebral artery 47
Anterior suprasellar meningioma 26 37
Arachnoiditis optochiasmatic 43
Arteriosclerotic arteries 43
Asymptomatic suprasellar meningioma 18
Atrophy optic 25 38

Blistering 45

Calcification 45
Carotid angiography 47
Central scotoma 28
Chiasmal syndrome 8 33
Chordoma 42
Classic symptoms 8

Diaphragma sellae 18 37
Differential diagnosis 38
Diplopia 20
Duration of symptoms 27

Ectopic pinealoma 42
EEG 27
Effective visual acuity 11
En plaque meningioma 54
Epidermoid 42
Erosion 45
Ethmoidal meningioma 10
Ethmoiditis suppurative 44
Extrasellar tumours differential diagnosis 39

Failing vision 19 38
Field score 11
Foster Kennedy syndrome 25 40
Frequency of suprasellar meningioma 10

Glioma 42

Hallucinations 20
Headache 26
Histopathology 37 62
Hyperostosis 45
Hypophysis – hypothalamus 26 56 57

Intrasellar meningioma 18
Intrasellar tumours differential diagnosis 39

Laminagraphy 45 50
Localization exact 37

Meningitis 44
Mental changes 26
Metopirone test 26 59
Mortality operative 57
Multiple meningiomata 55
Multiple sclerosis 44

Non paretic diplopia 20

Operation indications for 52
Operation technique of 53
Ophthalmoscopy 25
Optic atrophy 38
Optic foramen enlargement of 45
Optic foramen meningioma of 42
Optochiasmatic arachnoiditis 43
Origin of meningioma 7 37

Papilloedema 25
Pareses extraocular muscles 20
Periocular pain 20
Pneumography 49
Postoperative death 56
Pregnancy influency of 27
Pre-operative findings 27

Radiography 45
Recurrence 62
Retinal arteries 26
Retrochiasmatic meningioma 37
Results immediate 60
Results late 60
Rhinopharyngeal tumour 42

Scanning 50
Sex distribution 17 36 61
Size of tumours 36 62
Sphenoidal meningioma 40
Spinal protein 27
Stages 4 of Cushing 7
Sub-diaphragmatic meningioma 18
Subjective symptoms 19
Survival 62

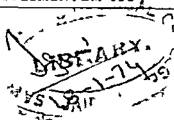
Temporal constriction 19
Treatment 52

Visual acuity 20 21
Visual field defects subjective 20
Visual field defects objective 22 39

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SUPPLEMENTUM 122



GENETICS AND PHYSIOLOGY OF COLOUR VISION

("MY STORY ON COLOUR VISION GENETICS AND PHYSIOLOGY")

by
GEORG H M WAALER
(From the institute of forensic medicine University Oslo)

MUNKSGAARD
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INDEX

		Page
Summary		7
Sections		
a	The two pair theory of Hering	11
b	Calculation on frequencies of colour blindness	12
c	Colour blind males	14
d	Colour vision of the conductors	16
e	Colour blind females	17
f	The one locus hypothesis The one-cistron hypothesis	19
g	An interlude	21
h	The pure green points on the spectrum	22
i	Modification of the one-cistron hypothesis	26
j	The pure blue points on the spectrum	28
k	Crossing-over between the G and B loci	29
l	New types among the normal trichromats anomal trichromats and dichromats	30
m	Demonstration of the genotype of conductors	37
n	The valence curves for green and yellow	39
o	The colour vision region	41
p	Concerning the three different cones in the retina	44
q	The physiology of colour vision	56
r	Electroencephalography and electroretinography	67

SUMMARY

This essay is the author's story of his interest in colour vision There are two main periods in the story the first from 1917 to 1927 and the second from 1965 to 1973 During the intervening years the author had the subject in his sub conscious and often reflected upon colour vision but plans for re-examination and a more throrough study of some of the problems were not realized until after the retirement

1 The heritable gene of colour blindness is sexlinked, i e located in the X chromosome Calculations on this basis showed that if the frequency of colour blindness among males is x the expected frequency of colour blindness among females would be x^2

2 There are four (six) types of colour blindness as discriminated by testing with the anomaloscope protanopia and deuteranopia these individuals are termed dichromats protanomaly and deuteranomaly these individuals are called anomal trichromats and they are often mentioned as colour defective not colour blind A fifth and a sixth type are called extreme protanomaly and extreme deuteranomaly With the abbreviations used the frequencies of the four types were found to be approximately 1 per cent Pp 1 per cent Dp 1 per cent Pl and 5 per cent Dl in an investigation of a group of slightly more than 9 000 boys

3 It was shown that the four types were not phenotypical variations of one genotype but they turned out to be dependent upon four particular genes, thought to be alleles i e located on the same locus in the X-chromosome (the author's one locus theory)

4 Females could then as they have two X chromosomes, have ten different genotypes with the above mentioned abbreviations Pp/Pp Pp/Pl Pl/Pl – Dp/Dp Dp/Dl Dl/Dl – Pp/Dp Pp/Dl Pl/Dp and Pl/Dl

5 Females analysed through their male relatives to be of the three first genotypes showed that Pl dominated over Pp i e the individuals with the genotypes Pl/Pl and Pp/Pl had the same phenotype protanomaly Females demon

strated to be of the three next genotypes showed that Dl dominated over Dp The most important result was that females of the four last genotypes had normal colour vision

6 The last mentioned fact completely explained why 0 44 per cent colour blind girls were found after an examination of a group slightly greater than 9 000 girls, and not 0 64 per cent colour blind females as would have been expected using the above mentioned calculations - $(0\ 08)^2 = 0\ 0064$

7 Since olden times females with a gene for normal colour vision in one X chromosome and a gene for colour blindness in the other have been called conductors, and because the first gene usually dominates over the second they have normal colour vision A question which for a long time had been at the back of the author s mind was Can these conductors, who were expected to be approximately 15 per cent of all females, be found in a mass investigation? A method whereby these conductors could be diagnosed is described and discussed in section m

8 Males with normal colour vision on two different points of the spectrum at about 515 and around 525 nm wavelength, find that the colour is pure green not blue green or yellow green These two types are called G_1 and G The properties are dependent upon two alleles in the X-chromosome also called G_1 and G_2 Females have three genotypes G_1G_1 G_1G and G_G_2 There are also three phenotypes designated G_{11} G_1 and $G_{\ 2}$ as the heterozygotes G_1G_2 have their pure green point varying around 520 nm Investigations in families, (father mother and children) confirmed this hypothesis on the mode of heredity and a special method for diagnosing these groups of individuals is described in section h.

9 Males with normal colour vision also have two different points for their pure blue neither lilac nor blue green These types and corresponding to the above the genes in the X-chromosome are called B_1 (blue point around 486 nm) and B (479 nm) In the same way as for the G properties the females have three genotypes B_1B_1 B_1B and B_B_2 and also here three phenotypes B_{11} B_1 and $B_{..}$ as also here the heterozygotes had an intermediate reaction Here also investigations in families proved the hypothesis on heredity

10 Individuals were also found with intermediate readings in relation to G_1 and G males These were called G_m (m from Greek mesos meaning intermediate)

11 It was postulated that the G_1 gene could mutate and the property degenerate to Pl (protanomaly) and further to Pp (protanopia) It was also postulated that the G gene could mutate and the property degenerate to Dl (deuteranomaly) and Dp (deuteranopia) Indications for these postulates were found in the points for pure green for the anomalous trichromats and the neutral points for the dichromats These points were for the G_1 (515 nm) and protanomal and

protanope individuals at shorter wavelengths than for the G (525 nm) deuteranomal and deuteranope individuals Types degenerated from the G_m type designated mesanomal (Ml as Pl and Dl) and mesanopes (Mp as Pp and Dp) were also found

12 The designation one locus theory was changed to one cistron theory and the picture of the genes was modified and extended to Fig 7 in section 1 Here the genes G_1 and G in the same cistron were thought to be on two points i e two loci (two mutons) the mutations to anomaly and anopia thus being made in two different DNA molecules This modification of the old one locus theory to the new one cistron theory was partly made because it was found that the most natural explanation for the new types G_m Ml and Mp was that the gene G_m gene possessed both particular constructions assumed for G_1 and G individuals (The G_m males in their reactions showed interesting similarities to the females with the genotype G_1G)

13 It was also possible to fix an individual s point of pure yellow being neither green yellow nor orange and his point of pure red where the sensation of orange disappears from the side of shorter wavelengths From an observer s green point to his red point (both these points are for a G_1 observer at shorter wavelengths than for a G observer) there is a yellow valence curve In the same way From an observer s blue point to his yellow point (both at shorter wavelengths for a B observer than for a B_1 observer) there is a green valence curve Both these curves are supposed to have a maximum of sensation of yellow and green respectively in the middle and with decreasing sensation of the colours against the four pure colour points See especially Fig 8 in section n

14 These valence curves are studied in relation to the three different types of cones which by their pigments are thought to absorb light of wavelengths corresponding to red green and blue and therefore coined erythrolabe chlorolabe and cyanolabe cones The absorption curve for the chlorolabe cones corresponds to the green valence curve The absorption curve for the so-called erythrolabe cone corresponds to the yellow valence curve The author has therefore renamed this to a chololabe cone It was further postulated that the cyanolabe cone not only has an absorption curve as shown in Fig 9 in the beginning of section p but also at the other end of the visible spectrum termed here as a porphyrolabe curve See Fig 12 later in section p

15 The absorption of light by pigments in the rods and cones leads to the conversion of light energy into chemical and electrical energy The author is not concerned with the first details of this change of energy form but the final result is believed to be a transfer of positive electricity (Na^+) from the outer part of the receptors where the pigments are localized in the discs to the inner part and further from the inside to the outside of the receptors and towards their outer end This results in hyperpolarization of the receptors cones and rods

16 Na^+ may be transmitted through the synapses to the bipolar cells whereby the potential between the outer and inner side of the cell membrane normally in the order of +70 mV is decreased i e the result is a depolarization

17 Furthermore the positive electricity (Na^+) is transmitted via the synapses to the ganglion cells where a kind of chain reaction is produced Na^+ passes rapidly inwards at the first Ranvier constriction causing a spike The Na^+ rush and spike building repeat at each Ranvier constriction and thus impulses pass along fibres in the optic nerve to the lateral geniculate nucleus

18 The electrical and chemical effects described in paragraphs 15 to 17 are thought to be characteristic for the rods the chololabe and chlorolabe cones The passage of electricity in the cyanolabe cone (as in paragraph 15) does not trans mit Na^+ through the bipolar synapses by excitatory buttons but according to the author s ideas negative electricity (Cl^-) by inhibitory buttons and the same occurs over the synapses to the ganglion cells

19 Analysis of wavelengths and thereby discrimination of colours thus takes place in the bipolar cells This analysis is continued in the fibres of the optic nerve where it is postulated that there are (at least) two different types of fibres which convey the stimulus effects from the chololabe and the chlorolabe cones respectively In these two types of fibres the effects from these cones summate with the stimulus effect from the rods whereas in both types of fibres the effect from the cyanolabe cones hyperpolarization in the bipolar cells (Cl^-) results in an inhibition of the spike building and thus subtracts from the effect from the rod stimulation (not summation) Thus four different sets of information arrives at the LGN summation and subtraction in both cholo nerves and chloro nerves A full description of these ideas is found in section q

20 Passage of Na^+ from the outer to the inner part of the receptors will in the electroretinogram give a small early positive wave (not demonstrated in the ERG of this investigation) The passage of Na^+ on the outside of the receptors to its outer end gives the so called a wave which is negative The transport of Na^+ over the synapses to the bipolar cell and via the synapses to the ganglion cell is th- most natural explanation for the important positive b-wave These are the interesting parts of the ERG in the point of view of this essay The most im portant postulate in the author s discussion in section q is the passage of Cl^- from the cyanolabe cones via the bipolar cells to the ganglion cells This should give a (heretical!) negative b wave In the author s opinion a comparison of the ERG picture with light of wavelength 552 nm (the maximum of yellow and green stimuli the maximum of photopic sensitivity) and of the ERG picture with light of wavelength 451 nm (near the maximum of the cyanolabe absorption curve) shows that there probably is such a negative b wave in the last case After this con tinuation of the negative a wave there follows seemingly a positive b wave which is explained as an effect from the rods which are recognised to give a delayed positive wave

21 This essay begins with investigations on heredity of colour blindness and of different types of normal colour vision These different G and B properties (paragraphs 8 and 9 in the summary) leads to the description of the green and yellow valence curves (section n and paragraph 13) From this point the author enters the physiological domain of colour vision (a new territory for him where he was inexperienced) and through theoretical discussions in sections p and q the author is led to some new ideas and in section r (paragraph 20) the investigations indicate the correctness of these ideas It might be as a proof for the author although it may not be so for others

a The two pair theory of Hering

This story and my interest in colour vision began in the spring of 1917 when I was a medical student at the eye department of the University Hospital Our teacher the great ophthalmologist Hjalmar Schiotz, showed us how a purple or a violet flower when moved out into the peripheral field of vision changed to pure blue and how a green yellow floral leaf changed to pure yellow at ap proximately the same distance from the central field and then exclaimed while closing his eyes and moving his grey head to and fro There must be two pairs There must be two pairs! In this way he indicated the two pair theory of Hering

Since that time I have always been an adherent of the theory of Hering in spite of the fact that the majority of the scientists writing upon colour vision were adherents to the tri-component theory Hering s theory seemed to me to be the natural one because it possessed all elements of describing the real nature of colour vision When I said above that this theory seemed to be the natural one I had in mind the simultaneous change of the two components in each pair as already hinted above The fields of vision of green and red are the same or near so the fields of vision of yellow and blue are practically the same under the *conditions of equal size and equal luminosity of the object We also find such a* coincidence in colour vision deviations during pathological conditions i e by acquired not hereditary colour deficiencies (Linksz, 1964 Chapter XII) yellow and blue being affected by diseases in the outer layer of retina green and red being affected by diseases in the inner layers and in the optic nerve (Kollner 1912) Furthermore we can never have a sensation of a green red colour or the sensation of a blue yellow colour The two components of each pair balance and cancel one another We can never see the two colours of each pair at the same time on the same spot or field

Goethe had already seen how each part of the pair counterbalance the other they neutralize each other but also produce the other on the borders and as after images (Linksz, 1964) Goethe looked through a prism Newton sent a beam of light through a prism One needs a screen to observe Newton s spec trum Everybody can see it Goethe s spectrum is literally in the beholder s eye

Only the beholder can see it It is not so surprising that the physicists cannot accept or do not like such a subjective experiment But colour vision is a subjective phenomenon

Later in section p I shall show that we have just these four pure colours blue green yellow and red All other colours are mixed Why we have just these four pure colours and why and when they give us the sensation of being pure I shall also explain there and in section q

I should like to further discuss the phenomenon to which I hinted above concerning the coincidence of colour vision fields for blue and yellow and also the coincidence for the fields for green and red However – as mentioned by Duke Elder in his Vol VII pg 416–417 (1962) if stimuli of sufficient intensity are employed the colour fields are approximately equal and coextensive with the white field This seems interesting to me We know that the cones are found also in the peripheral part of the retina so why should we not have a sensation of colours there? This is of course a question of threshold values corresponding to the second quotation from Duke Elder (l c) When the intensity of stimulation is decreased on an equal energy basis the colour fields contract proportionally interlacing with each other

This seems to contradict my teacher s demonstration as an indication of the two pair theory of Hering But as the third quotation from Duke-Elder shows if one measures the intensity of illumination not on equal energy basis but as equal subjective intensities and use great targets (20 mm²) we will see that the fields for complementary red and green are coincidal and so are the fields for complementary yellow and blue Thus in my opinion the demonstration of Schiötz is upholded as an indicator of the two pair theory

An apparent proof for the correctness of the tri component theory was given by the demonstration of the three types of cones in retina the erythrolabe the chlorolabe and the cyanolabe cones For me however it was on the contrary a proof of the incorrectness of the classical tri component theory as will be shown later in this story in section p

In section c I shall point out how the use of the anomaloscope for the diagnosing of particular types of colour blindness demonstrates a pitfall in the tri-component theory which has given the ophthalmologists their (misleading) terminology for the types of colour blindness

b Calculation on frequencies of colour blindness

The second item in my story occured in the autumn of 1919 when Ingolf Schiotz (1920) (son of the above mentioned Hj S) asked me if there could be a correlation between the frequency of colour blindness among males and that occurring among females The answer might be If the frequency in the population of X chromosomes with the gene for colour blindness is x then the frequency of

colour blind males will be x and the frequency of colour blind females x^2 because both X-chromosomes of these females must have the gene for colour blindness (The frequency may be 0 1 (10 per cent) then x^2 is 0 01 (1 per cent))

My answer was a little more complicated at that time I thought it easier for a geneticist to understand and accept There will be three different genotypes among females because they have two X-chromosomes, where the gene for normal colour vision and the allelic gene for colour blindness are located Two X chromosomes with normal genes give of course normal colour vision and two X-chromosomes with the gene for colour blindness should give the property of colour blindness The individuals of the third type with one X chromosome of each kind the heterozygotes have been called conductors since olden times, because they conduct the colour blindness to their sons without themselves being colour blind In a population where there is little migration of colour blind individuals the frequency among males of colour blind males (x) and the frequencies among females of conductor females (y) and colour blind females (z) will keep constant The frequencies of the two types of married couples in the population with a colour blind father and a colour blind mother or a conductor mother will be x z and x y respectively All daughters will be colour blind among the first type of married couple and half of the daughters will be colour blind in the other type Therefore the frequency of colour blind girls will be

$$z = xz + \tfrac{1}{2}xy = x(z+\tfrac{1}{2}y) \qquad (1)$$

In a similar way independent of the father's X-chromosome all sons of a colour blind mother will be colour blind whereas only half of the sons of a conductor mother will be colour blind Therefore the frequency of colour blind boys will be

$$x = z + \tfrac{1}{2}y \qquad (2)$$

Adding these two results we find that $z = x^2$ (as above)

Futhermore we can find that the frequency of the conductor girls will be

$$y = 2x - 2z \qquad (3)$$

These three equations are mutually interdependent that means that we cannot find the three unknown frequencies from these three equations But if we give x a value we can find the connected values of z and y As examples were given (Waaler 1927)

The frequencies

x (c bl males)		y (conductors)		z (c bl females)
4 per cent	corresponds to	7 68 per cent	and	0 16 per cent
6 per cent	corresponds to	11 28 per cent	and	0 36 per cent
8 per cent	corresponds to	14 72 per cent	and	0 64 per cent
10 per cent	corresponds to	18 00 per cent	and	1 00 per cent

In particular I would like to point out the figures of 8 per cent colour blind males and the corresponding 0 64 per cent colour blind females With these frequencies in the population 14 72 per cent every sixth or seventh female will be a conductor

Such frequency calculations are a daily proceeding now a days in genetical institutions (among others in an institute of forensic medicine where calculation of the frequency of different genotypes in blood groups and serum types are used to give a probability expression for a man to be the father of a child in a dis cussed fatherhood case) But Linksz (1964) in his book on Color Vision writes Waaler first made us ophthalmologists understand the fact that the numbers given for the frequency of color blindness in the male and in the female are not unrelated

c Colour blind males

In the school semester 1925/26 we come to the third and most important item in my story At that time I investigated the incidence of colour blindness in 9 049 boys and 9 072 girls attending schools in Oslo (II to VIII class)

During the first stage of the investigation I screened the pupils by getting them to read through an Ishihara book of pseudo isochromatic tables whereby I could easily pick out those who read as green and red colour blind or defec tive and those who showed some degree of uncertainty Both these groups were thereafter called to a closer investigation in which a Nagel s anomaloscope was used

In the anomaloscope the observer looks into a tub where he will see an illu minated circular plane The lower semi circle is illuminated by a yellow light with a wavelength of 589 nm The intensity of the yellow light can be regulated by a knob or screw The upper semi circle is lit up with a mixture of red and green The relative amounts of red and green can be changed by a device called a Vier ling diaphragm which increases the amount of green as it cuts down the red component and vice versa the sum of the quantities of red and green being con stant The regulation is made by a mixing knob from 100 per cent green 546 nm mark 0 on the screw to 100 per cent red 670 nm mark 73

By using these two knobs the one for the intensity of the yellow light the other for mixing of red and green it is possible to make the two semi circles look alike An individual with normal colour vision will have for instance mark 16 on the

yellow intensity screw and mark 38 on the mixing screw This may be written 38/16 and is called the Rayleigh equation This point is usually very sharp and only a slight twist of the screw will give the observer the sensation of dissimi larity We do not find such a well defined point in colour blind subjects They differ in four (six) different ways The four groups are called deuteranomals protanomals deuteranopes and protanopes As determined by the tri component theory the two last mentioned types are called dichromats They were thought to have lost respectively the second (deuteros) and the first (protos) of the three assumed colour receptors (components) the green and red respectively and these two groups were supposed to be blind either to green or red according to the theory

When we study the equations for the so called dichromats we discover the pit fall of the tri component theory Both types of individuals the protanopes and deuteranopes usually accept the Rayleigh equation When we make the upper semi circle more green they may both obey the equation also here by increasing th intensity of the yellow light They will also accept the equation out into the pure green (with no mixing of red in the anomaloscope) but here the protanopes must use a much greater intensity than the necessary yellow intensity for the deuteranopes Likewise we can move from the normal equation into red with a greater mixing of red in the upper semi circle as far as to 100 per cent red Both types also obey the equation here but they must make the yellow lower semi circle darker the protanopes making it much darker than the deuteranopes do The difference between the two types is quite clear The most important fact, however is that the so called red blind is also green blind and under certain circumstances he also finds that green and yellow are alike A so-called green blind is also red blind for him red and yellow are also alike during certain con ditions The translations from protanopia to red blindness and from deuteranopia to green blindness are erroneous The adherents of the tri component theory are in error from the start when using anomaloscopic testings by supposing that the protanopes have lost the first (protos) receptor and the deuteranopes have lost the second (deuteros) receptor Parenthetically I may add Let them be called dichromats they have only the possibility of recognizing two colours yellow and blue They have not lost either red or green but perhaps most of both

The so-called anomal trichromates do not accept the normal Rayleigh equ ation With a proper intensity of the yellow light in the lower semi-circle the protanomals and deuteranomals obey equations in the upper semi circle at points where the normal sees red (orange) and green (yellow green) respectively They are supposed to be – according to the theory – red weak and green weak and they are often termed colour defective and no colour blind In my essay (1927) all four groups were called colour blind (Rot grun blind) In addition two further groups are separated the extreme deuteranomals and the extreme prot

anomals with reactions between the respective anomals and anopes They were in 1927 grouped together with the deuteranomals and protanomals respectively

By loss or change in the third receptor one might suppose that one would get tritanopia and tritanomaly But there is no place for tetartanopia in the tri component system There is however in the literature some uncertainty as to the systematic position of tritanopia Is there identity of the congenital tritanopia and hereditary dominant optic atrophy? (Krill Smith & Pokorny 1970 and 1971) Therefore I shall not discuss these defects further although I once (in 1969) made some speculations about tritanopia and tetartanopia

When this material (the 18 000 school children) had been collected their family members (brothers sisters and parents) were called in for investigation in particular families of all the colour blind girls and in cases where I had found at least two colour blind brothers in the school investigation

The first conclusion appeared when I obtained results on conductor mothers and their colour blind sons The conductor mothers had normal colour vision (see next section however) and it was expected that half of their sons would be colour blind These 55 mothers had

in	2 cases	3 protanope sons	in	2 cases	3 protanomal sons
in	3 cases	2 protanope sons	in	7 cases	2 protanomal sons
in	1 case	4 deuteranope sons	in	4 cases	3 deuteranomal sons
in	3 cases	3 deuteranope sons	in	27 cases	2 deuteranomal sons
in	6 cases	2 deuteranope sons			

Furthermore I found three sister conductors with 2+1+1 sons (i e cousins) all four deuteranomal two conductor sisters with 2+2 sons (cousins) all four protanomal two conductor cousins had 2+1 sons (second cousins) all three protanope Two conductor sisters had 1+1 sons both protanope one mother had a protanope son a protanope brother a protanope male cousin and a protanope female cousin Finally I found a boy and his mother s father who were both extreme deuteranomal

With this very large material of conductor mothers with their colour blind sons I was able to postulate that the four (six) types of colour blindness cannot be one property with phenotypical variations It can not be one single gene that gives these types they must be a result of four (six) different and separate genes In earlier literature cases were also found of like types in each single family

d Colour vision of the conductors

The next group of problems arises from the study of the colour vision in the conductors themselves It was and still is accepted that the 'normal gene do minated over the colour blind gene thus giving these conductors normal colour vision However the question arose (as it had done before in the literature) as to

wether this dominance was complete Already in the first school I had registered two girls who reacted with *uncertainty in the Ishihara testing* but reacted as normals with the anomaloscope although their reactions in some degree were fluctuating and some times different during repeated testing being not so sharply and distinctly *repeated as was usually the case Both these girls had a deuteranomal* brother their mothers thus were conductors With the probability of 0 5 the two girls could have received the same gene from their mother Thus there was a *clear possibility of these two girls being conductors and I guessed that their un*certainty during testing with Ishihara and the anomaloscope could be a sign of their conductor constitution Later I found similar cases But not all conductor mothers who proved to be conductor as demonstrated by deuteranomal sons could be shown to have any deviations from normality in Ishihara or anomaloscopic It could not therefore be said that the problem was solved In addition among conductor mothers with protanomal deuteranope or protanope sons I had no examples of uncertainty or deviations from the normal Much later 40 years afterwards the problem was taken up again (1967 1968 1969) and I found a method by which I could indicate the genotypic constitution one X-chromosome with the gene for normal colour vision and one with the gene for colour blindness (Sections g and m)

e Colour blind females

Out of the very large group of subjects tested (9 049 boys and 9 072 girls) I found that 8 per cent of the boys were colour blind According to my study of the relation of the frequencies among males and among females (section b) we could expect $(0\,08)^2 = 0\,0064 = 0\,64$ per cent colour blind girls However I found only 0 44 per cent This discrepancy of 0 20 per cent was completely explained by studying the four (six) subtypes of colour blindness and recalculating the ex*pectations*

The study includes the analysis of the genotype of the colour blind females Each could be analysed by diagnosing the type of colour blindness among their sons their brothers their father their maternal uncles and their maternal grand father For example a deuteranope father and a mother with normal colour vision *have a deuteranomal son and a deuteranomal daughter The colour blindness of* the son demonstrates that the mother is a conductor and shows the type of the recessive gene which the mother has (deuteranomal) The daughter has two genes for colour blindness one in each of her X chromosomes (one derived from her father and one from her mother) The gene from the mother is determined from the deuteranomaly of the son and that from the father is determined directly from the father s deuteranopia In this way the genotype of the daughter is analysed (deuteranopia/deuteranomaly)

In this way I could see of course that the homozygotes had the same proper

ties as the corresponding males With my abbreviations – Pp for protanopia Dp for deuteranopia Pl for protanomaly and Dl for deuteranomaly both for the ge nes and properties among males – I found that a Pp/Pp female a Dp/Dp a Pl/Pl and a Dl/Dl female were protanope deuteranope protanomal and deuterano mal respectively We see in Table 1 that no protanope girl was found in the school investigation However elsewhere in my material I did find females of this subtype The compounds Pp/Pl and Dp/Dl were protanomal and deuter anomal respectively showing that the gene for protanomaly dominated over the gene for protanopia and the gene for deuteranomaly dominated over the gene for deuteranopia But when there was a P in the one chromosome and a D in the other the female had normal colour vision Anyway they could not be found in a mass investigation

We have ten different genotypes for females (see Table 1) and when we start with the frequencies for the boys

0 88 per cent protanope
1 03 per cent deuteranope
1 04 per cent protanomal
5 06 per cent deuteranomal

8 01 per cent colour blind

we can calculate the expected frequencies for the ten types Instead of the arith metical problem $8^2 = 64$ we can have this problem

$(0\ 88 + 1\ 03 + 1\ 04 + 5\ 06)^2$

or practically $(1+1+1+5)^2$

If for the male frequencies we take $\pm$ one standard deviation we can calculate the expected female frequencies on this basis And from the frequencies we can calculate the expected numbers among the 9 072 girls The result will be seen in Table 1

Table 1 Numbers (N B not frequencies) calculated from the male frequecies

Female genotypes	Numbers calculated from male frequencies: + st dev	frequencies	— st dev	Found
Protanope protanope	0 87	0 70	0.55	0
Deuteranope deuteranope	1 18	0 96	0 77	1
Protanope protanomal	2 04	1 66	1 32	3
Protanomal protanomal	1 20	0 98	0 78	
Deuteranope-deuteranomal	10 94	9 46	8 06	36
Deuteranomal-deuteranomal	25.39	23.23	21 16	
Protanope-deuteranope	2 03	1 64	1.30	0
Protanope deuteranomal	9 41	8 08	6 84	
Protanomal-deuteranope	2.39	1 94	1.55	
Protanomal deuteranomal	11 04	9 55	8 15	

We seen that there are small differences between the findings and the expectations and as far as the analysed genotypes are based on the study of heredity in families, we may say that the statistical examinations were in accordance with the genetical studies

The important fact that females with these genotypes Pp/Dp Pp/Dl Pl/Dp and Pl/Dl had normal colour vision made me very happy at the time of discovery So 40 years later I was very glad and if I may say so rather flattered to read in a publication by *Linksz* (1964) Waaler was the first to give serious thought to the discrepancy between the expected 0 64 per cent for affected females and his actual value 0 441 per cent. With genius and perseverence he dug into the family pedigrees of afflicted females studying both the paternal and maternal background and came up with an explanatory hypothesis which is one of the most *brilliant and most remarkable solutions of a biological puzzle*

Linksz is also one of the most eager defenders of the two pair theory of Hering and thus on this basis we came into friendly contact

As an example of this biological puzzle and its solution I give here (in Fig 1) a genealogical table of a family which I (1969) found 40 years later

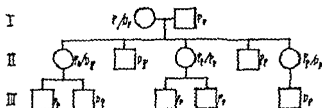


Fig 1 Pedigree of the colour blind family

The grandmother I 1 and her two daughters II 1 and II,5 all with the genotype Pp/Dp had normal colour vision

f The one locus hypothesis The one cistron hypothesis

The above mentioned fact the normal colour vision of the females with a P/D genotype had as I wrote at that time its most probable explanation in a two locus hypothesis The two alleles Pp and Pl and on the other hand the two alleles Dp and Dl should be located at two different places (loci) in the X chromosome The most usual thinking among the geneticists at that time was based upon the opinion of T H Morgan the founder of the drosophila school (1921) By crossing of two members of a series of allelomorphs the wild type will never come up but either the phenotype of one of the members or an intermediate type This would mean that if by crossing of two phenotypes one got the wild type (corresponding to the normal type of colour vision (?)) then the

two phenotypes would have their genes on two different loci This may be the reason why this supposition appears in the literature and is called Waaler s two locus hypothesis' In fact my opinion was quite the opposite, which will be seen in the continuation of the discussion Probably with some (a too great?) degree of caution I wrote I am tempted to speculate as follows

I thought of the gene as a giant molecule (a small laboratory or a miraculous workshop) which clearly could be thought to change (mutate) in different parts of the molecule I indicated these thoughts by a figure with five quadrangles (Fig 2)



Fig 2 Illustration of the old one locus hypothesis

If we place the first the complete quadrangle upon each of the other four we get a picture of the conductor type and find the explanation for the dominance of the normal gene over the genes for colour blindness i e one complete work shop produces the complete property The deuteranomal quadrangle upon the deuteranope or the protanomal quadrangle upon the protanope indicates how the smallest deviation from the normal is dominant the less deficient workshop manages the work alone However the deuteranomal and the protanomal quadrangle give a complete quadrangle as the sum It shows how a deficit in the upper right corner of deuteranomal is compensated by a full corner of protano mal and vice versa thus demonstrating the possibility of normal colour vision although the chromosome outfit is a compound s We see the same that is a complete quadrangle as the sum for the three other possibilities of the P/D geno types

Since that time this one locus hypothesis has in fact remained my favourite idea concerning this question In my opinion it was a preview or foresight of the modern cistron conception A cistron is as discussed in detail in section i just such a great molecule where there could be changes (mutations) at different points for example as clearly demonstrated for the hemoglobins If it is correct that my five quadrangles anticipated the idea of a cistron one may say that the great difference between the one locus hypothesis and a two locus hypothesis with two linked genes disappears If I postulate that P and D are located in the same cistron but at two different points in the great cistron then we may say that two different points are in fact two different loci But a locus in 1920 was all things considered tantamount to the gene in the thoughts of the geneticists and they did not think of the possibility of mutations at different points within the gene My Fig 2 was heretical at that time Today one will call this a cistron by definition the unity of developmental action A point within the cistron with the possibility of mutation is now called a muton by definition the unity of mutation The one locus hypothesis is therefore renamed the one cistron hypothesis or more complete the one cistron two muton hypothesis This will thus be my theory in the 1970 s I shall return in detail to this in the de scription of Fig 3 in section i and Fig 7 in section l

g An interlude

*During a period of nearly 40 years I made no further investigations into the sub*ject of colour vision (occupied as I was with pathology and forensic medicine) but I did have ideas laying at the back of mind concerning colour vision One question which most persistently returned in my consciousness was that men tioned in section d that is the colour vision of the conductors Was it possible to find a method of investigation by which we could detect and demonstrate the genotypical constitution of condutcors? During these 40 years it got more and more clear that genetical dominance was not complete in all instances Especial ly interesting was this experience obtained in medicine whereby it was important to recognize a recessive gene which could influence health in homozygotic state because it could be used in family counselling so as to find cases where both parents were conductors of a gene for malformation or an inborn error of meta bolism If both parents were such conductors they should have the probability of 1/4 of having such a child

When I retired (in 1965) I soon took up again my old interest in colour vision problems and I started an investigation upon the question of a method for the detection of the colour blindness conductor state I would like to mention this first trial although in fact it led to nothing in itself

From my school investigation protocol I picked out a large number of colour blind boys whom I could find in the telephone directory or in the address book

I then phoned them or went to their address (sometimes still the same address of their parents 40 years earlier) and asked Were you in the year 1925/26 a school boy in so and so class at so and so school? If the answer was Yes I had another question Do you have any daughters?

I succeeded in getting a great number of positive answers and very kind co operation In one case there were three protanomal brothers (in the school material) with 4+2+2 daughters All these eight cousins and many other girls (third generation from the parents of the school children in 1925/26) with colour blind fathers and who were therefore conductors at least came to the eye depart ment of the University Hospital where I had the possibility of testing them with different methods which I hoped would give a result One of the methods was to tire the observers with red or green colour and see if they would give Rayleigh equations different from the normal

However I did not obtain results which could be relied upon Nevertheless I have mentioned this part of my investigations because it is of some interest to show how good the possibilities are in such a small city as Oslo for making genetical investigations in the human population

In section m I shall return to the question of the diagnosis of conductors

h The pure green points on the spectrum

During these investigations on female conductors I was diverted to quite an other problem Rubin (1961) had found that observers with normal colour vision would point out two different places around 515 and around 525 nm respec tively as their pure green and not blue green or yellow green The first group included approximately 2/3 of all the males with normal colour vision

Some of my tests had hinted at such a bimodality of the unique green Pos sibly my way of testing with the anomaloscope was not the best one and as I was no expert on such investigations the individual statements of the green points were uncertain and variable But then I discovered a special method which could also divide the male individuals into two groups with the frequen cies 2/3 and 1/3 I suspected that these two groups were the same as the two groups of Rubin and control testings confirmed this Now propably a little biased I must admit I obtained a more certain division into two male groups by testing the individual green points

Later at the same time as I made this study Richards (1967) made some very nice exact and illuminating investigations which also confirmed Rubin s results

In my first paper (1967) I called these two properties among males protopia and deuteropia because I thought that the first group was related to the protano mals and the protanopes and the other group to the deuteranomals and deuter anopes In the same way as my protopes had their pure green point at a shorter wavelength (515 nm) than my deuteropes (525 nm) the protanomals had th ir

green points at shorter wavelengths (501 7 after Rubin) than the deuteranomals (519 6 after Rubin) and the protanopes had their neutral points at a shorter wave length (492 after Linksz) than the deuteranopes (498 after Linksz) thus there was a repeated and similar bimodality But after advice from Linksz we agreed to use the more neutral designation of G_1 and G (Linksz & Waaler 1968) Richards (1967) had called the two groups Group I and Group II respectively My G s meant to indicate green but all the same my names and Richards terms would go well together

My above mentioned special method requires an amplification of the descrip tion of the anomaloscope In section c I mentioned two knobs or screws one for the intensity of the yellow light in the lower semi-circle and one for the mixing of red and green in the upper semi circle By a third knob (the main knob) in model II of the Nagel s anomaloscope (from Schmidt & Haensch, Neumann Strasse 30 Berlin 62) (and now out of production) it is possible to change the yellow colour to shorter and longer wavelengths The two other colours red and green altered at the same time in parallel Hence it should be possible to find other equations I selected nine different points between 574 nm green yellow *on the scale 260 and 603 nm orange on the scale 240 where I in fact found* equations The fifth, the middle of these nine points was the usual Rayleigh equation point 589 nm on the scale 250 In Table 2 we find figures from my earliest investigations (1967) The figures on the line marked 'The brightness screw at were kept constant although the individuals could perhaps have found values which suited them a little better

Table 2 Average figures on the scale for the red green mixing screw (0 is green from *535* nm (at *260*) to *557* nm (at *240*)) (*73* is *100* per cent red from *645* to *695* nm (from 260 to 240))

The main screw at	260	257	255	253	250	247	245	243	240
The brightness screw at	17	18	18	17	16	14	12	10	7
Average for G_1 males	13.3	18.3	23 2	28 1	38 0	47 8	53 4	59 9	65.5
Average for G males	15 8	20 8	25 8	30 8	40 9	50 6	56 7	62 0	67 1
Average for G_1 females	13 9	19 0	23 7	29 0	38 9	49 7	56 1	61 4	66 7

There may be some overlapping on the single points for the individual obser ver In this regard it seems to me that the usual middle point (250) is particularly unsuitable for making a clear division into two groups This may be the reason why one does not find some sort of bimodality in mass investigations using the usual Rayleigh equation But by the use of all nine equations it is possible to diagnose the two different groups G_1 and G with greater certainty Three points may be sufficient If a testee at points 1 3 and 7 (260 255 and 245 on the main screw) sees likeness at the figures 13 23 and 53 respectively on the mixing

screw and at the same time is definite in rejecting 16 26 and 57 as likeness he will be a G_1 type A G individual will make the opposite observations

These results led me to postulate that the two types in males depend on and derive from a gene which appears as two alleles in the X chromosome which I also called G_1 and G Thus the properties in males and the genes were given the same designations Among the females there should be three genotypes – be cause they have two X chromosomes – G_1G_1 G_1G and G_2G I also found that there were three phenotypes which could be designated G_{11} G_1 and G_{22} The first and third reacted as G_1 and G males the second presumably the heterozygotes reacted in an intermediate way both as to their green point (around 520 nm) and as to their nine equations It will be seen from Table 2 that their reactions in the green part (points 1–4 260–253) are nearer to the G_1 reactions while those in the red part (points 6–9 247–240) are nearer to the G reactions The G_{12} females – with their postulated genotype G_1G – could therefore be diagnosed as such

By refering to Tables 3 and 4 I can show how investigations of the families confirmed this hypothesis

Table 3 The G diagnoses for mothers and their sons

Mothers	Sons	
	G_1	G
39 G_{11}	60	
35 G_1	39	35
11 G_{22}		15

Table 4 The G diagnoses for parents and their daughters

Parents	Daughters		
	G_{11}	G_1	G_{22}
35 G_1 x G_{11}	59		
22 G_1 x G_{12}	14	24	
3 G_1 x G_{22}		7	
12 G x G_{11}		20	
11 G_2 x G_1		6	11
7 G x G_{22}			13

Not all of the later investigators have found this bimodality among others Kalmus and Case (1972) They conclude Contrary to Rubin s and Richards findings but in agreement with Hurvich et al and Verriest no bimodality was found in the distribution of the spectral locus of unique green among male and female samples of normal trichromats and using several methods But further they write As no separate groups for pure green perception could be ascertain ed the question of a possible link with the sex linked modality in anomaloscopic readings as described by Waaler does not arise This last remark points of course at my supposed identity of Rubin s and Richards (and my) two groups with different spectrum green points and my groups as identified by the nine equations Kalmus and Case quite rightly remarked that if there is such a con

nection Rubin and Richards should not have found a clear bimodality because my heterozygotic females (G_t) would fall into the area between the two (overlapping) distribution curves

I wrote to Rubin and Richards and asked if they could clear up this problem

Rubin had unfortunately lost his old material but Richards could help me however He wrote I have re examined the unique green points for the 141 observers that I have collected to date The distribution for the males and females are plotted separately in the enclosed figures

These plots show the distributions For the males there are two groups with different averages for the wavelengths of the pure green 65 males in Group I had an average of 511 84 and 29 an average of 528 02 with two distribution curves without overlapping For the females there were in fact three groups, also here without overlapping 14 had an average of 506 57 20 had an average of 515 20 and 13 an average of 527 46 With a gene frequency of 0.50 for both G_1 and G in this sample of females we would expect 12 23 and 12 Therefore Richards concluded as follows Given the above qualifications the present data are consistent with your interpretation for the limited samples of females These above qualifications mean that his selection of females and males followed a different procedure and it is possible (for me to think) that they could be taken from different populations (Richards himself indicates Flemish extraction against Scandinavians?) this being a possible explanation for the frequencies 0.50 against the more usual (?) 2/3 and 1/3 The middle group of females, the assumed heterozygotes G_1 has not at all fallen into the area between the two male distribution curves but was hidden in the upper part of the male G_1 curve

As a consequence of this elucidatory re-examination which Richards has made of his material I shall adhere to my opinion of the identity of the two properties the spectral pure green and the sex linked anomaloscopic property studied by my nine equations I should point out that there are small differences between the averages of 512 and 528 nm of Richards from my around 515 and around 525 nm However not too much stress should be laid upon these differences For me as a geneticist the main point is the bimodality – two different properties and I have not on the whole really measured the wavelengths I have only taken the figures from a drawing given by the makers of the anomaloscope

However the two averages 512 and 528 for males and the three averages 507 515 and 527 for females could give me a base for the speculation of course bearing in mind the relatively small numbers of female observers that the two G_1 genes in the G_{11} females have a summation effect upon the shift from G and G_{20} averages The the G_1 effect for the G_1 females could be a pull down to 515 (instead of my 520 between 515 and 525) This is only speculative of course but it could nevertheless be an invitation for further investigations on a greater material

I Modification of the one cistron hypothesis

I still adhere to the one locus hypothesis but after having recognized the two types with different points of spectral unique green G_1 (first called protopia by me) and G (deuteropia) it is time for a modification of the one locus hypothesis or the one cistron hypothesis as we may call it now a modification which will bring it closer to modern thinking far in advance of that of the 1920s and which takes into account the chemical composition of the gene as well as the substances determined by the gene

It is now commonly known that somewhat simplified the gene is built up of a long row of nucleotides (DNA) It is also known that three neighbouring nucleotides code for one amino acid for instance 1 500 nucleotides construct a polypeptide of 500 amino acids This will often be enzymic in character and sometimes it will already be the property studied However in other cases there will be several links between the gene and the property As to colour vision the last link before the property may be a protein that produces the pigments usually thought to be the basis of the colour perception Such a protein will usually have a prosthetic group essential for the function i e the production of the pigments which change the light energy to chemical and electrical energy in the eye

From this simplified description of the connection between a gene and a property I especially draw attention to the prosthetic group and postulate that there are either two different prosthetic groups on the same place or the same prosthetic group is placed at two different points of the protein thus being decisive for the G_1 and G property respectively I shall return to these details at the end of section 1 and there discuss the two hypotheses two different prosthetic groups on the same place corresponding to two different trinucleotides on the same locus in the cistron or the same prosthetic group on two different places corresponding to two identical trinucleotides at two different loci in the cistron A protein of this construction will produce normal colour vision with two ways of seeing pure green Possibly there might be a change on the surface of the protein after mutation in the gene that will be the cause of the vision of an anomal trichromat Thus this could be the same decisive mutation for both protanomaly and deuteranomaly but on two different basic polynucleotides and correspondingly on the same effective and decisive part of the protein in two different base proteins There could also be another change on the protein surface and mutation at the same or another point producing a dichromatic colour vision and again possibly the same change and mutation on two different substances – protein and DNA – will give protanopia and deuteranopia respectively All this is plainly demonstrated in a figure from my 1967 a paper here Fig 3

This figure can illustrate both the gene and the protein shaped from the gene In the upper circles the P and D stood for protopia and deuteropia (as I used the names in 1967) now they may be changed to G_1 and G respectively They tell

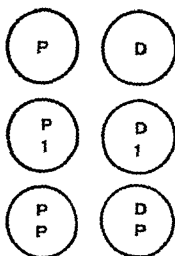


Fig 3 Illustration of the new one cistron hypothesis

us that the gene for normal colour vision has two allelic forms the one (P or G_I) giving the property of a green point at 515 nm the other (D or G_r) giving the green point at 525 nm in a male with such an X-chromosome As mentioned above for the prosthetic groups there are also two possibilities for the gene Either two different trinucleotides on the same locus or the the same conclusive (i e conclusive for the prosthetic group) trinucleotide at two different loci

The middle circles each have an l indicating the mutation producing protanomaly and deuteranomaly respectively

The lower circles each have a p indicating the mutation producing protanopia and deuteranopia respectively

We thus have the two rows of genes and properties among males

G_I – Pl – Pp green point at 515 nm – protanomaly – protanopia and

G – Dl – Dp green point at 525 nm – deuteranomaly – deuteranopia

This is in correspondance with my thoughts expressed in the 1967 paper that each of the two rows represents a family of properties as seen when we use the names proposed there

protopia – protanomaly – protanopia

deuteropia – deuteranomaly – deuteranopia

It is not in accordance with the reasons given for the proposal of the neutral names G_I and G (Linksz & Waaler 1968) but the similar bimodality of the green and neutral points as previously discussed in section h makes the theory of two such family rows of genes and properties among males a favourite idea of

mine However I shall adhere to the names G_1 and G because of their parallel ity to the names B_1 and B in the next section

We see that the hypothesis behind Fig 3 postulates that the mutations for protanomaly and deuteranomaly are at the same muton and are supposed to be the same chemical change in a trinucleotide (and correspondingly the same change in an amino acid derived from the nucleotide) but the two mutons are already included in the difference between the G_1 and G genes and thus the mutations for protanomaly and deuteranomaly are one and the same mutation in two different basic substances The hypothesis postulates mutatis mutandis the same for protanopia and deuteranopia Analysing the expression one cistron two muton hypothesis as proposed in section f we find that one-cistron has to do with the total property of colour vision two-muton has to do with the dif ference between G_1 and G As to protan and deutan they are one muton as just described but are on two different basic substances (See also Fig 7 in sec tion 1)

j The pure blue points on the spectrum

If we set both the yellow brightness screw and the mixing screw at 0 on the model II of a Nagel s anomaloscope we will only have the upper semi circle light ened by a green colour when the main screw is set at 250 By changing the set ting of the main screw we can find the green points at 515 and 525 nm at marks 281 and 271 respectively It is in this way that I tried to measure the green point for each individual observer

We can move the main screw for shorter and longer wavelengths to the blue and to the yellow and red We can then find that there are two different types of males one indicates the pure blue (neither green blue nor lilac) at around 487 nm the other type has the pure blue point at or around 479 nm It is easier to locate the point of pure blue than to locate the point of pure green Usually each individual will reject the other setting very decidedly I called these two proper ties B_1 and B and assumed that the two properties were dependent on and de rived from allelic genes in the X chromosome and also called the genes B_1 and B In accordance to the findings with the green point properties I found three phenotypes among females which clearly indicated three genotypes B_1B_1 B_1B and B_B the supposed heterozygotes having their blue point a little more variable around 483 nm These phenotypes could be designated B_{11} B_1 and B_{22}

There is independency of the property pairs A G_1 individual can be either B_1 or B and so can a G_ individual and this is the case with the same frequen cies which B_1 and B have in the total population

This supposition on the heredity of the B properties is confirmed by family investigations as demonstrated in Tables 5 and 6

Table 5 The B diagnoses for mothers and their sons

Mothers	Sons	
	B_1	B
22 B_{11}	36	
33 B_1	38	19
18 B_{--}		29

Table 6 The B diagnoses for parents and their daughters

Parents	Daughters		
	B_{11}	B_{1-}	B_{--}
18 B_1 x B_{11}	25		
18 B_1 x B_{1-}	14	16	
6 B_1 x B_{--}		10	
2 B x B_{11}		3	
12 B x B_{1-}		16	8
7 B x B_{-}			9

We see that both the sons and the daughters are found with the expected properties But if we scrutinize the figures for the children to B_1-mothers we find a great deviation from the expected 1 1 proportion As can be seen the 33 B_1 mothers have given a B_1 gene 38 times and a B gene 19 times to their sons and the daughters have received a B_1 gene 30 times and a B_- gene 24 times from their B_{1-} mothers 68 B_1 and 43 B_- in all A deviation of this magnitude or more has a probability of 0 03 (or little less by the chi^2 test) and thus is not impossible but I myself was afraid that some of the first tested mothers were wrongly diagnosed as B_1 instead of B_{11} The gene frequencies are probably 50–55 per cent for B_1 and 50–45 per cent for B

k Crossing over between the G and B loci

As the G and B properties both have their genes in the X-chromosome the question arises as to whether the genes are located at two different places or the genes are placed in one cistron This can be studied by calculating the frequency of crossing over as originally and extensively studied in the drosophila material

The so-called double heterozygotic females G_1 B_1 may be of two different genotypes G_1B_1/G B or G_1B_-/G B_1 This mode of writing indicates that the genes G_1 and B_1 in the first genotype are in one X-chromosome and G_2 and B_- in the other Such double heterozygotic mothers give us the possibility of detecting cases of crossing-over when the mother has more than one child whose G and B types are analysed These double heterozygotes may be analysed by the phenotype of their sons For instance if such a mother has a G_1B_1 son she is analysed to be of the first above mentioned genotype

I repeat from my 1968 paper two families

G_1B_1 x G B /G_1B_1 → G B + G_2B + G_1B_1/G_1B_1 + G_1B_1/ G_1B_1

G B_1 x G_1B_-/G B_1 → G B_1 +G B_1 + G_1B +G B_1/G_1B

In the first family the mother is analysed through the two G_-B_- sons and as we know that the daughters have received the father's G_1B_1 we see from their phenotypes $G_{11}B_{11}$ that they have obtained the same genes from their mother In the second family the mother is analysed through the two G B_1 sons whereas the third son and the daughter have received the G_1B gene from the mother

In none of these families is there any crossing over In the first family a G_1B son or a G_nB_1 son would have been a crossing over between the two X chromo somes of the mother and so would a G_1B_1/G_1B or a $G_1B_1/G\ B_1$ daughter

A third family seemed to be an important case

$G_1B_1 \times G_1B_1/G\ B \rightarrow G_1B_1/G\ B + G_1B_1/G\ B + G_1B_1 + G\ B_1$

The last son must if the diagnoses are correct be a crossing over And the con clusion was (1968) that in 22 families with double heterozygotic mothers and 59 children tested and diagnosed as to their phenotypes and genotypes as illustrated in the examples above there is one case of crossing over i e 1 7 per cent

But these two brothers and another brother pair formed the basis for the next section together with a father in one family and a son in another family studied in section m which deals with the problem of the diagnosis of female conductors

l New types among normal trichromats anomal trichromats and dichromats

As to the green point properties there were difficulties in a few cases in the classification of individuals according to their phenotypes I tried to make the diagnosis (G_1 or G among the males) in the most likely direction in all cases There were two pairs of brothers who rested in my mind I had written in my notes Both give curious uncertain and fluctuating answers 'They both react unusually and irregularly I had also earlier learned this sentence 'Take care of your exceptions' Meaning Keep them in your mind for future advantage'

I now tested these four young men again The first pair was the brothers just mentioned in the last section which was concerned with the crossing over prob lem where they were diagnosed as G_1 and G respectively As I see it now I ought to have been warned by their settings at the usual place for the Rayleigh equations at mark 250 on the scale for the main screw There the figures pointed at the opposite diagnosis for both It occurred to me that I might have used a biased way of examination of the nine equations in which the first fortuitously low (13) or high (16) (see Table 2) value on the mixing screw led me to expect correspondingly low or high values in the subsequent equations as well Both brothers were apt to find likeness in a broader zone not on a point as is usually the case so it could be easy for an investigator with a biased opinion to obtain the answers he expected This time I was aware of the possibility of a personal bias and I think the results now are more accurate

It now turned out (Waaler 1973) that the two brothers equation (not points but) zones were altogether similar to each other Instead of giving all the figures I shall present the results schematically in Fig 4 Corresponding to each of the nine equation points 260 257 255 etc there is a short vertical line marking out my personal G_1 reaction a point marking the average G reaction relative to the G_1 reaction and the zones of likeness for the two brothers also relative to the G_1 reaction The main impression from Fig 4 is that both brothers accept like

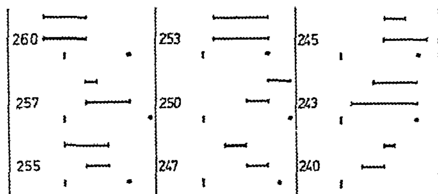


Fig 4 Picture of nine equations for two brothers with the new type G_m between equations for G_1 and G males

ness in a region between the G_1 and G averages but for the first four points the equation is near my G_1 values and for the last four or five points the equations are near the G values This picture has some similarity in principle to the reactions of the G_{12} or heterozygotic females (Table 2)

The other pair of brothers reacted in a similar way They seemed rather more uncertain with higher degree of variation than the first pair They both tired rapidly so I tested them only at the points 1 3 5 7 and 9 But altogether the picture was the same low zones on points 1 and 3 high zones on points 7 and 9

I propose to call this rare type and its gene G_m *The index could have been* 1½ (between 1 and 2 for G_1 and G_) but I chose instead m from Greek mesos, middle intermediate

In section i I hinted at two groups of properties connected with each other as a *family of relatives* I could postulate that the property and gene G_1 by mutation could degenerate to protanomaly and protanopia, and that the property and gene G by mutation could degenerate to deuteranomaly and deuteranopia.

What then will be the picture of a degenerating G_m? The records of my previous investigations contain cases which might provide an answer to this question

I had difficulties in specifying the colour blindness type in two male individuals hinted at in the end of section k and studied in the following section m on the colour vision of the conductors They were a father who demonstrated his daughter s conductor constitution by being colour blind and a son who demonstrated the same for his mother At that time it was enough for me just to know that they were colour blind For each of them I had written extreme deuteranomal (?) and protanomal or 'protanope (?) in my notes I was now interested in retesting them In the first case the father obeyed equations from ordinary Rayleigh equation far out in the green and red as protanopes and deuteranopes

usually do It was difficult or impossible for him to find likeness in the pure red with a usual darkening of the yellow semi circle as it is usually found in the case of true protanopes or deuteranopes But he accepted an equation for pure green 0/26 5 (0 indicating the pure green in the anomaloscope and 26 5 indicating the intensity of the yellow light) For the intensity of the yellow light the protanopes find values at around 40 and the deuteranopes at around 20 The value 26 5 is thus in the region between that which is usual for protanopes and deuteranopes With my nine equations (see Table 2) the father obeyed equations with some difficulty with a green and red mixed colour which was a little more green than is average for G_I individuals they being like the deuteranomals in this respect This would explain how I could suspect him of being 'extreme deuteranomal (?) In Ishihara tables 12 and 13, where normals read 26 and 42 deutans 2 and 4 and protans 6 and 2 he could at first see nothing but in clear daylight he was able to read 6 and 2 just as a protan In the Farnsworth Munsell 100 Hue Test he managed the arrangement as a normal individual which is quite extraordinary for a protanope or a deuteranope Thus he certainly has an uncommon type of colour blindness and could fit into a hypothetical degeneration or mutation from the G_m type This individual was himself an ophthalmologist and he told me that when he was a medical student the physicians in the eye department of the University hospital could not agree to his type of colour blindness

The son in the second case reacted in the following manner At the usual Rayleigh equation point he first accepted the protanomal equation (54/10) but it was also possible for him to accept a deuteranomal equation (20/20) and an equation out in the pure anomaloscopic green, 0/26 We notice here the same unusual reaction as for the case just analysed (0/26.5) With my nine equations it was very difficult for him to accept likeness especially if I (as I did in the other case) kept the yellow light at nine points as in my standard testings (see Table 2 the line 'The brightness screw at) With high red proportion in the mixed colour he could see the change from green to red and back again at relatively sharp points although he did not find true likeness but observed in the upper semi circle a red green colour or as much of red as of green But when I allowed him to change the intensity of the yellow light himself he was able with great difficulty to accept likeness with low red admixture in the green part of the nine equations and with high red admixture in the red part Thus he resembled the other case The same was true when he was tested with Ishihara where he red as a protan In the Farnsworth Munsell 100 Hue Test he did not manage the arrangement so well in fact I found an axis of faults as for a protanope and a suggestion of a deuteranope axis (I had the impression that he was not so care ful or did not exert himself so much as the other case in arranging the colours) Thus this other case is likewise an atypical colour blind case and might fit the hypothesis of a degeneration and mutation from the G_m type

Both the male individuals tested seemed to correspond to the anopes in their reactions In the same way as G_m individuals (with normal colour vision) found equations between the equations for G_1 and G males (see Fig 4) so my impression was that both males gave reactions between the deuteranopes and the protanopes I could therefore call them mesanopes and the property mesanopia A presumed gene for the property could be designated Mp (as Pp and Dp)

But could we now find the corresponding anomalous individuals? I had in my mind a new type (1969) with nine equations between the equations for normal G_1 individuals and for the usual deuteranomal individuals In the green part of the nine equations (at 260 with the main screw) they gave values near to those of the usual deuteranomals At the ordinary Rayleigh point (250) they fitted equations near the lower point of the normal variation I called this type Low degree deuteranomaly and designated the gene Ld I now retested two of these individuals and tried to see if it was possible for them to accept protanomalous equations but without success When the observer himself used the screws for mixing the red and green and for the brightness of the yellow light he always ended at a sharp point where he found likeness between the two semi-circles In my protocol I had three other individuals who had given similar reactions I calculated the averages of the equation values at my nine points In Fig 5 I have drawn two straight lines (with three mm distance on the graph paper) describing the nine equations for G_1 and G individuals Using the same scale on the paper I have drawn the corresponding lines for the protanomals of the deuter anomals above and below the lines for the individuals with normal colour vision

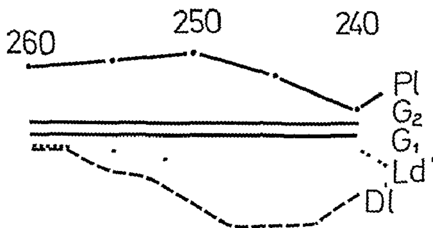


Fig 5 Illustration of the average values of the equations for the new mesanomal type in relation to averages for protanomaly G_1 G and deuteranomal males

If a line is drawn for the Ld individuals we find that the equations are always between the G_1 and Dl lines But at the same time we see that these Ld equations are found between the Dl and Pl ractions and we also see that in the green part 260-255 on the main screw they are nearer the Dl reactions whereas in the red part at 240 they are nearer the Pl reactions This is in fact the same relationship that we found for G_m between G_1 and G (see Fig 4)

I shall therefore assume that the low degree anomalous type in fact is the anomalous degeneration from the normal (but seldom) G_m type I call the individuals mesanomal and the type mesanomaly and the gene could be designated Ml (as Dl and Pl)

I shall propose that we withdraw the name Low degree deuteranomaly (Ld) and keep the name mesanomaly for this property and call these individuals for mesanomals Thus I postulate a new row and three new types between the two rows on Fig 3 in section 1

Phenotypes	Normal trichromates with reactions between those of G_1 and G	---- mesanomal	--- mesanope
Genotypes	G_m	Ml	Mp

In this connection I should like to return to the problem of the hypothetical prosthetic groups on the protein which is the last link in the chain between the gene and the property This prosthetic group is supposed to be a decisive factor for the production of the pigment which is responsible for the transformation of light energy to chemical and electrical energy in the retina

The prosthetic group may be associated with a particular amino acid This amino acid originates more or less directly from a trinucleotide in the gene I said in section 1 that the prosthetic groups for the G_1 and G property could be either two different groups on the same place or the same group on two different places These new types the G_m and its Ml and Mp relatives favour for me the latter hypothesis Then we would have an important trinucleotide in the gene material on two loci for the G_1 and the G gene respectively and the decisive prosthetic group on two possibly not too distant places on the surface of the responsible protein The reason why this is a pet idea of mine is that I could then propose to have this particular trinucleotide and hence this decisive prosthetic group on both places at the same time This would give a good explanation for the new properties We may now take a repeated look at Fig 3 with its six circular planes We now place three new circles between the two rows of three and then take out the three uppermost circular planes and write there the full description of the idea as hinted at above

In the first circular plane G_1 The decisive prosthetic group as well as the producing trinucleotide in the gene has a particular locus

In the third circular plane G The decisive prosthetic group as well as its producing trinucleotide has another particular locus

In the second i e the new middle circular plane G_m There are two decisive prosthetic groups as well as their two producing trinucleotides on both the particular places noted for the two other circular planes

In the three middle circular planes one could then just add the l below G_1 G_m and G and in the three lower circular planes add the p in the same way

The upper three circles show us the three different basic proteins on which the changes l and p will give the three different anomalous types and the three different anopic types

The Gene G_m might be the result of an intracistronic crossing-over between the two genes G_1 and G by a mother with the genotype G_1/G_2. But what would be the effect of the other X-chromosome? The gene G_m could as well be produced by a mutation of a G_1 or a G gene



Fig 6 Illustration of crossing over between the G_1 and G genes

I like to reproduce the above discussed extension of Fig 3

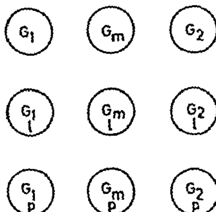


Fig 7 Modification of Fig 3

It is interesting to note that the heterozygotic females G_1/G phenotype G_1 and the G_m males where m in fact according to my theory should mean 1+2 have a similar way of reacting on my nine equation points Near the G_1 values at the points 1–4 (the green part) and nearer to the G values at the points 6–9 (the orange part) I would like to also point out that the described Ml individuals also have the same relation to the Dl and Pl individuals in the nine equations near to Dl in the green part and near to the Pl in the orange part Similarly the females with the genotpe Pp/Dp have normal colour vision (see Fig 1) and the male first described as Mp where M would mean P+D shows his indication of normality in the Farnsworth Munsell 100 Hue Test

The mesanomal and mesanope types described above could very probably correspond to some types described in the literature the so-called 'non allelic compound hemizygous males supposed to have both a protan and a deutan gene in one X-chromosome Thus they have the same explanation as the males of mesanomaly and mesanopia that is G_1 and G in one X chromosome Thus if this comparison is correct only the G_m type is really new

It is also obvious that this hypothesis can explain cases where females with normal colour vision may have sons with different types of colour blindness For instance a female with these two cistrons in her X chromosomes

G_1 l and G p

will usually have a protanomal son (G_1 l) or a deuteranope son (G p) But after a crossing-over between the G loci and the l p loci she may have a protanope son (G_1 p) or a deuteranomal son (G l)

A female with these two regions in her X chromosomes

G_1 l and G_1G_+ p

may have sons of these four types protanomal mesanope (after crossing over) protanope and mesanomal

(Later in section o (The colour vision region) I shall introduce the concep tion of a region meaning two or more adjoining or neighbouring cistrons where the different cistrons have related tasks for instance production of the green and blue point properties At this point in the story it is not necessary to make the distinction between the terms cistron and region)

I also like to add the following in relation to the Ml (previously called Ld) gene In my 1969 paper I discussed some quotations from my record of in *vestigations from 1925/26 and found that females thought to be of the geno* type Dl/Ld now Dl/Ml gave Rayleigh equations between the normal values and the values for the deuteranomals Furthermore Ml males would give Rayleigh equations near the lower value of the normal variation of the Rayleigh equations and *thus could be diagnosed as having normal colour vision (also reading Ishi* hara as a normal) Then as a normal father to a deuteranomal daughter this could be a (mistaken) case of 'penetrance of the recessive gene in a female sup-

posed (wrongly as it turns out) to have the genotype N/Dl (N = normal colour vision) whereas the genotype in fact is Dl/Ml

A further addition In a table in the 1969 paper I supposed that a female with the genotype Pp/Ld would have normal colour vision because we have a P in the one X chromosome and a D in the other But if we change the Ld to Ml the supposition of a normal colour vision would not be the logical conclusion This would be more in accordance with an actual case (in my 1969 paper) thought to be Pp/Ld that is now Pp/Ml (her father was Ld now called Ml) and this daughter reacted as an irregular protanope

Furthermore in addition to the Ld problem In the 1927 essay it turned out that all except one of the fathers of the colour blind daughters were colour blind The suggestion that the exception was not the real father was discussed During the intervening investigations (see section g) I tried of course to find this family in order to perform a re test but was without success

m Demonstration of the genotype of conductors

I now return to the question of the possibility of diagnosing female conductors i e to prove or at least more or less indicate that one of the X chromosomes has a gene for colour blindness This is a problem that I have already mentioned in my 1927 paper and which rested in my mind until I started anew in 1965 and which I have hinted at here in the interlude (section g)

For the females who have a Dl in one X chromosome we can assume that they have in their other X chromosome a G_1 or a G allele (influencing the green point) and both these types of conductors may be a B_1B_1 B_1B or B B_ genotype (influencing the blue point) Thus we shall have in all six different genotypes for the Dl conductors Similarly we shall have six different genotypes for each of the Pl Dp Pp extreme deuteranomal and extreme protanomal conductors 36 different genotypes in all and in addition now twelve for the Ml and Mp conductors They may not differ in phenotypes and I shall not try to analyse them all (I made in fact some trials in the 1967 paper) My main point will be limited to the general problem that is will the conductors estimated to be around 15 per cent of all females (if the groups Ml and Mp males were 1–2 per cent of all males the frequency of conductors would be 16–18 per cent) show any signs that differ from normality? In other words will the normal allele be completely dominant or not?

In an attempt to answer these questions I performed three experiments

1 I noted the fact that the mother II 1 in the colour blind family (Fig 1 in section e) could read Ishihara tables X and XI which normals should not be able to read that in table IV she could read the figure 2 as expected of the colour blind as well as the normally seen 5 and in table V she could read 21 as the colour blind as well as 74 as the normal Therefore I went through the classes

in a school and tested girls with these tables The 15 girls (out of 156) picked out in this way could be tested with the anomaloscope as could their parents If these 15 were conductors the father should be colour blind in half of the cases In the other cases the mother ought to show the signs of a conductor constitution But in the six families I investigated it turned out that only one of the fathers was colour blind (Dl) and only one of the mothers showed reactions that could indicate a possible conductor constitution The result of this first experiment was therefore disappointing

2 I noted in the 1969 paper (on the pure blue points) that the colour blind alleles seem d to influence the placing of the point most plainly for the colour blind males but also for the conductors The three genotypes B_1B_1 B_1B and B_2B_2 had their normal blue points around 487 483 and 479 nm Colour blind males of the two types B_1 and B had their blue points at 490 and 482 nm Working on the assumption that the females have two functioning systems reacting at the same time it could be expected that the conductor females with the three mentioned blue point genotypes would have their blue points at 488 5 nm for the B_{11} females (the middle of 487 and 490 half of 487+490) 484 5 for the B_1 females (half of 487+482 or 490+479) and 481 5 for the B ₙ females (half of 479+482) Later in section p I shall give a possible explanation for this influence of the genes for colour blindness

In this experiment I therefore tested all girls with regard to their localization of blue points and picked 18 out of 86 In the eight cases where I tested the parents I found only one colour blind father (protanope) In two families the mother showed the above mentioned possible signs of a conductor constitution One of these mothers had a colour blind son the other had a colour blind uncle (her mother s brother) and a colour blind nephew In the other five families I found only normality These five girls were probably B_1 and therefore their blue points will always be difficult to fix exactly Thus the second experiment was also disappointing

3 In the third experiment I paid special attention to the anomaloscope equations I used here only numbers 1 3 5 7 and 9 of the nine equations the first four being the most important As mentioned earlier we usually find points of likeness When we find zones but not points of likeness that is three or more degrees on the mixing knob we would suspect such a girl to be a conductor This experiment turned out to be rather successful and among 94 girls I recorded 20 with these hypothetical signs of the conductor genotype

In two of the cases the parents were separated but in the 18 cases where I tested the parents I found eight colour blind fathers (one who later turned out to be mesanope one a deuteranope one a protanomal one an extreme deuteranomal two deuteranomals and two who later turned out to be mesanomal) In all the other ten families the mother expressed the same signs as their daughters of

a conductor constitution One of the mothers had a colour blind son and thus was certainly a conductor In three other families the tested girl had a sister with the same signs as herself and her mother

Therefore with due allowance for a reasonable margin of error I think I have found a method for finding conductors by mass investigation I do not claim that the method is infallible It might happen that we shall not detect them all Conversely the original group earmarked for this experiment had three more than the 20 mentioned But when the three girls were tested with their normal parents I found that the girls now gave reactions which could not form the basis for a suspicion of the conductor genotype They had in the first testing (a mass investigation we might call it) given the impression of zones, but this was probably due to their inexact way of identifying likeness or my inexact way of testing them for example letting them say Stop a little prematurely

It is obvious that in mass investigation which is set up to find conductors one may on the one hand verify the diagnosis by finding a colour blind father or son or have a real probability by finding other colour blind males in her family and on the other impair the diagnosis by not finding such colour blind males

n The valence curves for green and yellow

In the same way as we can fix an individual s pure blue point on the spectrum (see section j) it is possible to point out his pure yellow point, which is usually very sharp When we set both the brightness and the mixing screws at 0 and then regulate the main screw towards longer wavelengths we come to a yellow illumination of the upper half of the circular plane in the anomaloscope With only a slight twisting of the main screw the observer will perceive a hint of green on the side of shorter wavelengths and orange on the other side Usually a B_1 observer has his pure yellow point at longer wavelengths than a B observer with averages at 583 and 581 nm respectively

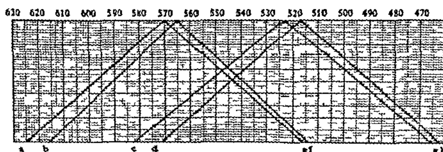


Fig 8 Sketches of two green valence curves and two yellow valence curves Abscissae (above) terahertz (= 10 sec⁻¹ for the frequencies) a and e end points for the green valence curve for B males b and f end points for B_1 males c and g end points for the yellow valence curve for G_1 males d and h end points for G males

Between an individual s blue point and his yellow point he has a sensation of green from a hint of green in the blue green near to his blue point (486 and 479 nm) via an intense sensation of green to a hint of green in the yellow green just before the yellow point (583 and 581 nm)

If we calculate the wave frequencies in terahertz (= 10^{12} sec^{-1}) for these four measures of wavelengths and suppose that the highest point is in the middle between the blue and the yellow points as measured in terahertz we obtain as seen in Fig 8 (from my 1968 paper) a green valence curve from b to f for a B_1 male and from a to e for a B_2 male The highest points are at 565 THz i e 531 nm and 570 THz i e 526 nm I know nothing of the form and height of these curves only the four points on the zero line It is probable that such valence curves have a certain similarity to an exponential distribution curve (see Fig 12 in the section p) And what is the meaning of the zero-line in the Fig 8? Also here I refer to the discussion of Fig 12 (from my 1969 paper)

It is not necessary to suppose that the highest points the greatest effect of a green perception mechanism correspond to the points of pure green

I have also indicated the pure red point of the observers One could say that there is no real red point It is certainly dependent upon the light intensity (Linksz 1964) and it is supposed to be placed in the infrared i e out of the visible spectrum In my opinion that which is placed in the infrared is a purple reception mechanism By regulation of the main screw (as for fixing the pure yellow points) to longer wavelengths with the intensity of light I use in the ano maloscope the observer will with not too great difficulty find a point where he perceives red without mixture of orange on the side of shorter wavelengths On the other side he has a feeling of darkening or greyness I myself sometimes have a feeling of something bluish and the same had the female II 1 in the colour blind family Fig 1 who has the genotype Pp/Dp This red point is the most difficult to fix distinctly the green point is easier the blue point better and the yellow point is the easiest I shall discuss why we have this sequence of distinctness in section p where we shall particularly discuss Fig 12 I find that G_1 and G_2 males have the averages of their red points at 645 and at 650 nm respectively

Between an observer s pure green point and his pure red point he has a sens ation of yellow from a hint of yellow in the green yellow near the green point (515 and 525) via an intense sensation of yellow to a hint of yellow in the orange near the red point (645 and 650 nm) In the same way as for the green colour we have a yellow valence curve in Fig 8 from c to g for a G_1 male and from d to h for a G_2 male Again in the same way The highest points are at 523 THz i e 574 nm and 517 THz i e 580 nm respectively

It is not necessary to expect that the highest points the greatest effect of a yellow perception mechanism correspond to the points of pure yellow

With regard to these yellow valence curves I also refer to the discussion of Fig 12 at the end of section p

A very important and for a geneticist interesting consequence of the study of these valence curves for green and yellow is the following

The gene G_1 produces a yellow perception mechanism with its specific (particular and typical) absorption point where the light on absorption is transformed to chemical and electrical energy, at 574 nm On both sides of this specific absorption point there is a diminishing effect until the vanishing points are reached (515 and 645 nm at the green and red points respectively)

The G_2 gene produces another yellow perception mechanism with its specific absorption point at 580 nm with a diminishing effect on both sides until the vanishing points are reached (525 and 650 nm at the green and red points respectively)

The B_1 gene produces a green perception mechanism with its point of specific absorption at 531 nm with diminishing effect on both sides until the vanishing points are reached (486 and 583 nm at the blue and yellow points respectively)

The B gene produces another green perception mechanism with its specific absorption point at 526 nm and diminishing effects on both sides until the vanishing points are reached (479 and 581 nm at the blue and yellow points respectively)

In principle we could discuss in the same way the production of the perception mechanisms from the genes for colour blindness that is colour vision deviations from the four just mentioned normal properties But together with the clarifying of the vanishing points I shall return to this in section p where I shall discuss Figs 12 13 and 14

o The colour vision region

Concerning the substances and the design of the gene my ideas have developed in a zigzag fashion as exemplified by the Figs 2 (1927) 3 (1967) and 7 (1973 a) My ideas today are based upon the conception of the DNA and the genetic code as briefly described in section i The locus in the 1920 s has developed into the cistron of the 1970 s I shall now present an illustration of the colour vision cistron or rather the colour vision region

When we define a cistron as the unity of developmental action we must imagine that only one property usually is produced by one cistron But two connected properties as the green point and blue point properties could be produced by two adjoining or neighbouring cistrons in one region We have already indicated this in section l

The genes l and p and their corresponding normal allele n will probably work through an enzymic protein which influences the relative effects of the chlorolabe and chololabe cones that is a protein unrelated to either the G or B proper

ties Therefore the most probable supposition would be the location in a third particular but neighbouring cistron in the same region

The final conception will be that the colour vision region contains three different cistrons one for B (B_1 and B_2) one with two mutons for G_1 and G plus the situation G_1G_n where both mutons are occupied and one for the colour blindness genes (n l and p)

Here it is natural to raise the question of whether the situation for the B genes could be the same as for the G genes that is one trinucleotide on two loci and the same prosthetic group on two different places on the surface of the protein this being decisive for the pigment production However to date no information exists which will give an answer to this question But if the answer is found to be affirmative in the future there will also be two mutons in the B cistron

As to the genes n l and p they are supposed to be responsible for the production of the proportionate (effect or) number of chlorolabe and chololabe cones The gene n is responsible for the normal relations and thus the yellow and green valence curves as in Fig 12 With the gene l there will be more chololabe and fewer chlorolabe cones The yellow valence curve will be higher and broader and the green valence curve lower and narrower Therefore the green points shift to shorter wavelenghts and the blue points influenced by the narrower green valence curve move to longer wavelengths Combined with G_1 we then have the property protanomaly with G_* the property deuteranomaly The distance between the blue points and green points is shortened from both sides The p gene will further increase the number of the chololabe cones and reduce the number of the chlorolabe cones and the distance between the green and blue point will usually disappear thus the neutral points are formed In combination with the G_1 gene we thus get the property protanopia with G the deuteranopia

A forth allele e could in similar ways produce extreme protanomaly and extreme deuteranomaly This would mean that we had four alleles n l e and p

Taken as a whole these ideas indicate the colour vision region in the X chromosome as being a big workshop containing three particular workshops that is three adjoining or neighbouring cistrons one for the pigments producing the B properties a second for the pigments producing the G properties and a third cistron which controls the relative numbers of cones

The two B genes may or may not be alleles

The two G genes are located in two mutons The distance between the two mutons within the cistron is not necessarily short neither is the distance between the amino acids which have reference to the property But when the polypeptide is converted to a globular protein these particular amino acids may come closer to one another on the surface of the protein However this neighbourhood will not give a measure of the possibility of crossing-over Such a neighbouring location for a chromophore could be the reason for two different angles

with the surface and thus explain why there are two different maxima of light absorption that is 574 and 589 nm for G_1 and G males respectively

As to the n l and p genes in the third cistron it was just mentioned that there might be four possible set ups for this workshop n l e and p

To the reader all this might seem too complicated and very hypothetical But it must be emphasized that all the specific genes are stepwise based upon the genetical investigations The two blue point properties indicate the green valence curves which in turn indicate the two different pigments in the chlorolabe cones In the same way we have the three steps the two green point properties the two yellow valence curves and the two different pigments in the chololabe cones Thirdly the movement of the green and blue points towards each other in the case of the transition from individuals with normal colour vision to anomal trichromats and dichromats indicates the changes of the relative importance of the chololabe and chlorolabe cones that is the supposed effects of the genes n l e and p

Genotypes					Nanometer averages for blue points	neutral point	green point	Phenotypes
1	2	B_1 or B	G_1	n	487 or 479		515	normal col vision
3	4	—»—	G	n	487 or 479		525	normal col vision
5	6	—»—	G_1	l	490 or 482		502	protanomaly
7	8	—»—	G	l	490 or 482		5_0	deuteranomaly
9	10	— —	G_1	p		492		protanopia
11	12	— —	G	p		498		deuteranopia
13	14	—»—	G_1G	n	497 or 479		(520)	norm col vis (G_n)
15	16	—»—	G_1G	l	490 or 482		(511)	mesanomaly (Ml)
17	18	—»—	G_1G	p		(495)		mesanopia (Mp)
19	20	— —	G_1	e				?extr protanomaly?
21	22	—»—	G	e				?extr deuteranomaly?
23	24	—»—	G_1G	e				??extr mesanomaly??

Table 7 The region no 1 is that of a normal G_1B_1 observer (with blue point at 487 nm) no 2 is that of a normal G_1B observer (with blue point at 479 nm) Further for instance nos 17 and 18 show the genotypes of a mesanopia male with the calculated neutral point at 495 nm The six last genotypes (19–24) are the genotypes e No stress should be laid upon the sequence or distances for the cistrons and mutons as they are unknown The nanometer figures in parenthesis on the table are not found through testing of observers but are calculated as middle points 520 in the middle between 515 and 525 511 between 502 and 520 495 between 492 and 498 The basis for these calculations is the phenomenon that the new types G_m Ml and Mp usually give reactions between those for the G_1 and G_2 males and that will be in accordance with the supposition of the double occupation of the two mutons (G_1G) for these types of colour vision

Table 7 illustrates the question of deutan protan crossing over The B cistron is of no interest in this instance A female with no 5 in one X chromosome and no 11 in the other may have protanomal and deuteranope sons without crossing over An intra-cistronic crossing-over between G_1 and G can give a mesanope son An inter-cistronic crossing-over could give a protanope or a deuteranomal son The probability of an inter cistronic crossing over must be supposed to be greater than that of an intracistronic crossing-over

Crossing-over cases reported in the literature will be more closely studied in a following paper

One cannot be completely satisfied with this table The fact that deuterano maly is more frequent than protanomaly although G_1 is more frequent than G requires an explanation It is to hope that future studies and calculations might give a more satisfactory picture of the colour vision region

If the number of region pictures is 24 as in the table (or 18 with exclusion of the last six) how many genotypes will we then have for the females? The answers are 300 (and 171)

p Concerning the three different cones in the retina

In recent research (Rushton 1958 1962 Marks 1963) a 'proof' for the tri component theory has been adduced in the finding that three different cones in the (human) retina have their maximum of sensitivity towards light rays at 577 540 and 447 nm (Fig 9) These three types of cones are designated erythrolabe chlorolabe and cyanolabe The names are meant to indicate that the cones capture the red the green and the blue Here we have a pitfall in the tri-component theory Because we have three different cones they must in the opinion of the adherents to the tri component theory correspond to the three colours red green and blue But at 577 nm there is no sensation of red As we move along the spectrum away from the red end the sensation of red in fact disappears completely at approximately 580 nm On the other hand if we take a look at Fig 8 we find that my yellow valence curve has its calculated and supposed

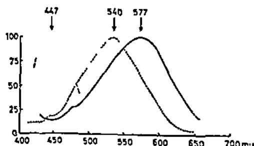


Fig 9 Absorption curves for the three types of human cones the cyanolabe the chlorolabe and the erythrolabe

maximum at 574 and 580 nm for G_1 and G individuals respectively That fits well with the absorption curve for the so-called erythrolabe cone It therefore seemed appropriate for me to rename this cone a chlololabe cone as it captures the yellow light The erythrolabe chlorolabe and cyanolabe cones are therefore not a proof of the correctness of the tri-component theory On the contrary the erythrolabe cone proves that the theory is in error on this point The tri component theory rests upon the demonstration by phycicists since the days of Newton on the fact that it is possible to give the impression of all possible hues of colour by the mixing in appropriate propertions of three standard colours as defined by wavelengths and if the three standard colours are conveniently selected I have never understood why this demonstration by the physicists should necessarily have been applied to the eye and to human colour vision in particular

Thomas Young (1775-1825) the founder of the undulatory theory of light and the tri component theory said in 1802 that the three colours were red yellow and blue but he had already by 1803 substituted yellow and blue for green and violet Since that time yellow has not been supposed to be a suitable standard colour in this connection Of course the findings of the physicists are correct and have their own value but it is their direct application to physiology that is wrong At any rate it is illogical to base a theory solely upon physicists experiments I have learnt from Linksz (1964) to lay stress upon the emphasis of the difference between stimuli and stimuli effects and I have found that Duke Elder (1968) points at the same In contrast to radiometry which is concerned with measurements of the energy of light and is a problem for the physicist we have the photometry which is the subjective measurement of light as perceived by the eye and is a problem for the ophthalmologist I quote The physiological *responses belong to an order of things completely different from physical stimuli* They are not linearly derived from them but are released by them Physiological effects produced by light are therefore completely different from its physical properties

If you call the erythrolabe cone chlololabe and if you admit that a tri-component theory has nothing to do with the studies and demonstration of the mixing by the physicists of three standard colours (or that your theory should not be based on these mixing experiments) you can certainly keep the conception of a tri component theory but it will not be the classical tri-component theory And I shall point out what the adherents of the tri component theory have also admitted that is from the bipolar cells and all the way to the cortical center of vision the human nerve system works in the spirit of Hering s two pair theory What we perceive with our consciousness is produced according to this two pair theory

As for the cyanolabe cones there is in fact a sensation of a violet colour at 447 nm not blue Marks Dobelle and MacNicholl (1964) also noted that the

three maxima do not correspond to red green and blue but to yellow green and violet I suggest that these cyanolabe cones give a perception of both blue and red I have thought that what is at the outside of the yellow and green valence curves gives us the impression of blue to violet and of red to purple

At the spectrum point at wavelength 894 nm (or 890) at twice that of 447 nm (or 445) I assumed that we have the effect of a red and purple mechanism That this true red is not in the visible spectrum is in accordance with the investigation of both the physiologists and the ophthalmologists (Linksz, 1964) In my opinion it is right to remark that it is not red but purple which has its maximum of ab sorption in the infrared But it is only the left shoulder of such a distribution curve for the purple absorption which is functioning in the visible spectrum that is functioning in the human eye

At wavelength shorter than 479–486 nm the blue points and at wavelength longer than 645–650 nm the red points the cyanolabe cones may be the only ones in traceable action for colour perception They may in fact act over the whole of the visible spectrum but between 480 and 650 nm their effect is com pensated and inverted by the two other types of cones I shall return to these ideas and in the end of this section make an explicit interpretation of this puzzle

Parenthetically but of interest and importance it may be noted that three groups of cones have also been demonstrated in goldfish with maxima at 455 530 and 625 nm (Fig 10 from Marks 1963) In Fig 11 we find pictures of the receptor potentials for the two types of bipolar cells in goldfish retina (Svaetichin 1956a Svaetichin and MacNichol 1958) The two maxima in Fig 10 455 and 625 nm which we may interprete as being due to cyanolabe and erythrolabe cones correspond to the peaks of the two oscillograms in Fig 11 The two lowest points in Fig 11 we find at 490 and 570 nm Between these two points at 530 nm we have the third maximum in Fig 10 which is due to what we may call the chlorolabe cones meaning the cones with the intermediately placed absorption curve in Fig 10 Because every bipolar cell is connected to many cones (or at least two) th^ effect of different cones will accumulate in one bipolar cell Therefore we can follow the effect of light of different wavelengths in Fig 10 Moving from the left we have (or rather the goldfish has) a sensation of blue until around 490 nm where the counteraction of the cones with absorption maximum at 530 will give a sensation of an other colour Moving from the right there will first be a sensation of red until around 570 nm where the same will again happen I do not know what these sensations of an other colour will be probably some thing like our green We see that these points of alteration in colour perception 490 and 570 nm correspond exactly to the facts in Fig 11 the minima in the oscillograms The sum of the two oscillograms in Fig 11 is at a minimum at 530 nm which in Fig 10 is the maximum for what we might call the chlorolabe curve



Fig 10 Absorption spectra for the goldfish cones

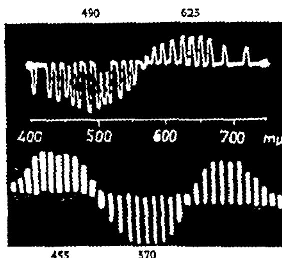


Fig 11 Receptor potentials for two types of bipolar cells in the retina of the goldfish

In goldfish the cone which produces the middle curve of the three in Fig 10 is assumed to have the double effect of counteracting and reverting the effect of the other two cones I have hinted above to a similar effect of the cyanolabe cone in man Thus although the particulars are different in goldfish and man the principal pattern of the function according to a two pair theory may be the same Let me therefore postulate a similar hypothesis for the human cone ab

sorption curves Absorption of course in this connection means that the light energy is transformed to chemical and electrical energy

Parenthetically I shall dwell upon the quoted works of Svaetichin (1956a and b) He finds three different cones in fish the one is a luminosity mechanism (called L) the other two of particular interest here called R–G and Y–B showing depolarization and hyperpolarization (conf Fig 11) at different regions of the spectrum corresponding to the opposite effect of red and green and of yellow and blue An important fact is the demonstration of twin cones which must be so intimately connected that one gets the two reactions depolarization and hyper polarization expressed even if the electrode all the time is placed only in one of the twins

From the first of the two papers I quote 'As far as mammals are concerned Walls suggested that during their evolution they have spoiled a colour vision mechanism already perfected by their ancestors and that the primates were forced to develop it anew This makes it clear for me that one shall not base thoughts on human colour vision automatically and directly upon results derived from investigations on fish as I have suggested above a similar but obviously different hypothesis for the human cones It is remarkable that twin cones are not described in the human retina But here I like to quote from Svaetichin (1956c) The striking similarities between colour vision in man fish and other animals support the view that the peripherical mechanisms for colour vision in the whole animal kingdom are built essentially upon the same functional principles i e the twin chromoreceptors We read here how Svaetichin has written this paper in honour of Hering But as we have no twin receptors (anatomically) in the primates (the animals of interest for me) their role in man must be taken over by pairs of cones (physiological twin receptors see next section q) and bipolar cells

In the other paper (1956b) Svaetichin says mentioning the work of Granit (1947) that his modulators are difficult to understand because most of his work is made on the colour blind cat and Svaetichin quotes Walls again In short Granit is convinced that he is dealing with a colour mechanism whereas I have been convinced for a decade that he is not

For me this comes in contrast to Duke Elder s (1968) mention of Granit To him we are indebted for most of our understanding of this aspect of the intimate sensory mechanism of the vertebrate retina Granit (1947) earlier found nar row spectral bands which he called modulators and assumed that they formed the basis for the qualitative discrimination of colours Such bands found in the frog by Granit and Svaetichin (1939) were at 460–480 500–530 and 580–600 nm as we see nearly corresponding to the three cone absorption curve maxima in my Fig 12 450 535 and 570 nm It is not self evident that frog and man have exactly the same pigments and I should therefore rather say that Granit has been 20 years before his time in finding these narrow bands In his book (1947) Gra

nit mentions the regions for the modulators 440–470 520–540 and 580–610 nm *still nearer to the human figures Granit has investigated a great variety of ani* mals tortoise (1941a) rat (1941b) fish (1941c) frog (1941d) guinea pig (1942a) pigeon (1942b) snake (1943a) and has found different bands which it will not be necessary to scrutinize here Concerning the cat (1943b) he mentions the maxima 520 and 560 nm and says If they are colour blind they can either be deuteranope (with the luminosity curve as for the normal) or protanope (with the luminosity curve shifted towards shorter wavelengths) In my opinion the colour blind also have their colour vision mechanism so the findings do not contradict Granit s modulators as a basis for colour perception

For the full elucidation of these points of disagreement, I should like to quote from an other book written by Granit (1955) Cats are generally held to be colour blind which may or may not be true The point I have raised is not necessarily dependent upon the extent to which this animal uses a mechanism of colour per ception that may well be rudimentary and damped by scotopic and photopic dominators which with rare exceptions are the onlv ones that have been obtained in this animal with the aid of single spikes For be that as it may the essential point here is to establish experimentally the fact that a single spike is capable of transmitting different types of information by utilizing the frequency code Per haps I have used the frequency code in the next section

Finally I would like to point out that Granit (1945) found seven modulators in the cat with maxima at 600 580 540 520 500 460 and 440 nm However he found that there were three groups of modulators two red yellow three green and two blue violet corresponding to the tri-component theory The sum of the effects of all these modulators seemed to be similar to the effect of the postulated photopic dominator

In connection with the supposed colour blindness of the cat and with these seven modulators which Granit had found in the cat I should like to mention some *ideas which have been stimulated by reading Monod s paper (1970) (I have* only read the Norwegian translation) Selection and retention of advantageous mutations which come up by chance in the course of hundreds of millions of years are dependent upon the pattern of living for the particular species of ani mal Thus the cat as a nocturnal animal will (probably) have the advantage of being able to discriminate between regions of wavelengths There we can se the meaning of Granit s seven modulators in the cat But the cat will not necessarily have the conscious impression of colour as we have (!) It is more probable that the cat only utilizes the modulators as suggested by Granit Modulators provide cues for discrimination of wave lengths Finally one more quotation from the book of Granit (1955) on his dominator modulator theory Still less is it claimed that the theory can give any information as to whether or to what extent an animal may possess colour vision

After this parenthesis on the works of Granit and Svaetichin I return to Fig 11 from which we learn that there are two different types of bipolar cells each of them reacting in two different opposite ways in their dependence upon wave lengths 455 nm in contrast to 570 and 490 nm in contrast to 625 This is a way of working exactly in accordance with the two pair theory of Hering For my 1969 paper I was told by an expert that a similar situation exists in the ganglion cell axons of the optic nerve There are two groups of nerve fibres each reacting in two opposite ways depending upon the wavelength obviously also in ac cordance with the theory of Hering Now by the repeated use of these im portant physiological facts in the optic nerve we are not able to find the relevant works to quote But for me the work of Wiesel & Hubel (1966) which I shall discuss in the next section (q) points in the direction of there being two such groups of nerve fibres They have studied the responses over the synapses of the single cell in the lateral geniculate nucleus It may be that not all centripetal fibres fall into these two groups But I have anyhow based my discussions on what follows on such a bimodality of the nerve fibres in the optic nerve But anyway it is very probable that a number of axons from the ganglion cells only carry the effects from stimulated rods It is also possible that some of the fibres in the optic nerve are connected to only one type of cone not this pair cone connection which is described above as the most important postulate

I remarked that the goldfish curve with a maximum at 455 nm in Fig 10 has a secondary maximum around 600 nm as illustrated hypothetically in Fig 12 where I have used the maxima 445 535 and 570 nm from Marks Dobelle and MacNicholl (1964) I assumed further that the cyanolabe curve continues in the direction of an infrared maximum at 894 nm outside the visible spectrum where the frequency is half the frequency (in terahertz THz) at the cyanolabe maxi mum

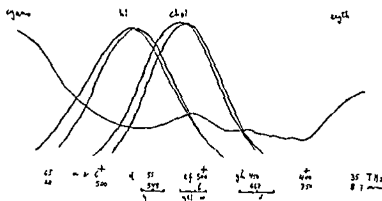


Fig 12 Proposed picture of the absorption spectra from the chlorolabe (B_1 and B_2) the chololabe (G_1 and G_2) and the cyanolabe cones of males with normal colour vision

The two points 673 and 337 THz (447 and 894 nm) correspond to a musical octave If the absorbing substance (pigment) in the cyanolabe cones has its typical resonance at the frequency 674 then the frequency 337 THz will reach the substance every second of the typical time The musical fifth, fourth major and minor thirds will reach the substance every third fourth fifth and sixth of the typical time respectively I assume that the fifth (the quint of the musicians) corresponds to the mentioned secondary maximum and I have also indicated the fourth and major and minor thirds on the line for the cyanolabe effect The most important of these hunches is that of the deep octave whose left shoulder is within the visible spectrum

When I use music terminology I do not mean to say that this octave and this quint etc are explained as resonance in the same way as for the acoustical waves As we are here dealing with the transmission of light energy it will be more reasonable to use the aspect of the corpuscular theory of light. For the waves at 400 and 800 nm (750 and 375 THz) there will be the same numbers of photons when the energy at 400 nm is twice that of the energy at 800 nm With this aspect it will probably be easier to accept a possible connection between the effects of light of these two wavelengths

I would suggest that the cones which react in accordance with the green valence curve (the chlorolabe curve) are connected with one type of bipolar cell and through them with one type of ganglion-cell axon in the optic nerve The result of a stimulus to the cone will be an effect in one direction in the nerve fibre The cones which correspond to the yellow valence curve (the chololabe curve') are connected with the other type of bipolar cell and the other type of nerve fibre and thereby give an effect in the same direction The cones with the hypothetical and complicated light absorption curve from cyanolabe to its deep octave are assumed to be connected to both types of bipolar cells and through them with both types of fibres in the optic nerve and thereby will show effect in the opposite direction of the two other cones as described above I shall return in detail to these hypotheses in the next section where I shall study the chemical and electrical occurrences in the cones the bipolar cells and the ganglion cells with their axons

At this point of my story I shall only elucidate the meaning and thoughts behind the picture in Fig 12 Reading from left to right along the curves we shall first have a feeling of violet, the stimulus of the cyanolabe cones showing the effect in both types of nerve fibres in the optic nerve From beneath the peripheral part of the green valence curve will counteract the red in violet until the blue part remains alone (in one of the types of axons in the optic nerve) at the two blue points for the B and B_1 individuals We then have the effect of green and blue until the blue is cancelled by the yellow valence at the two green points for the G_1 and G individuals only the green being here in function We then

have the effect of green and yellow up to the yellow points from the right the red part of purple has here cancelled the effect of the green valence only yellow being in function Then we have the sensation of orange until the red points where from the right the blue part of purple has cancelled the yellow valence here The red part has remained alone in the one type of axon which is present in the optic nerve From there we have the sensation of darkening or perhaps a bluish colour We see here exactly the explanation of the 'mysterious' eight vanishing points described by Fig 8 in that they are points of cancellation These points of cancellation show us the four pure colours which I have earlier describ ed in section a On both sides of the green valence curve and on both sides of the yellow valence curve we have the crossing points with my hypothetical cyano lobe valence curve Thus it is a consequence of this picture in Fig 12 that we shall have just four pure colours and vice versa we may say that the fact that in the visible spectrum we find just four points with sensation of pureness indi cates that the main aspect of this figure is correct An why do we have this sens ation of pureness? Because on each of these points there is only one activity in the optic nerve only one of the just mentioned two opposite reactions in each of the two types of axons In the next section I return to this and describe these four happenings in the axons of the optic nerve

In Fig 12 we thus find the meaning of the zero line of Fig 8 This line is now replaced by the hypothetical line for the cyanolabe absorption curve The 'zero will here be the points of crossing with the other valence curves If this is so the (eight!) zero points are not all on the same level With the assumption of a sym metrical form of the green and yellow valence curves this may lead to other calculated places for the maximal and specific absorption points For instance the middle distance between a and e (Fig 8) that is the place of maximum for the B_3 green valence curve will possibly not be ½ (625+516) THz = 570 THz, that is 526 nm as calculated for Fig 8 but at shorter wavelength because point a has a higher position than point e

The above points reminded me of two sentences read in the book of Linksz (1964) Increasing illumination increases the relative share of the yellow com ponent in the prosensation and whenever the intensity is increased in the long wave end of the spectrum we find an increasing yellowishness The long wave as described here means from the red end of the visible spectrum to 507 nm as we go from 507 nm to the violet end of the visible spectrum an increasing bluish ness results from an increase in illumination At three points there will be no change in hue with changing illumination One of the three points lies at 574 nm which is exactly at my calculated maximum for the G_1 yellow valence curve Perhaps the psychological feeling of yellow cannot be more (or less) than the maximum therefore there will be no change in hue The second point of no hue change is (after Linksz) at 507 nm This is natural because on the one side we

may have an increasing yellowishness on the other side an increasing bluishness But does this border point at 507 nm, indicate something for the green valence curve? Probably not and anyway not necessarily But one might speculate that, with the intensity of light which I have used in my anomaloscope the crossing of the yellow valence curve will be at 515 nm for a G_I male that is at his pure green point (as also found by Rubin (1961)) but with greater intensity of light it could be found at shorter wavelength, as the averages of Richards (1967) indicate 512 nm for G_I males and 507 nm for G_{II} females The third point of no hue change is at 476 nm I have no definite explanation for this in relation to Fig 12 and my calculations We find 476 nm at shorter wavelengths near my pure blue points at 479 and 486 nm for B and B_I observers respectively Perhaps an increasing illumination in this region will first intensify the green effect, bringing the blue points a short way to shorter wavelengths but then in competition with the increasing bluishness stop at 476 nm These three points with no hue change at 574 507 and 476 nm should be compared with three points of stable colours mentioned by Duke Elder (1962) 574 495 and 471 nm (as they after Duke Elder are found by Hess 1891 Engelkind, 1921 and Aulamo 1925)

The above discussed influence of increasing illumination touch on another part of Fig 12 At the base of the figure we have three horizontal lines indicating the regions of the nine equations for the green yellow and red slits in the anomaloscope Above the green region we notice that the yellow valence curve is higher for a G_I male than for a G male Thus the G_I individual gets a relatively greater share of the yellow component I think this will mean a relatively smaller share of green Thus he must add more green in the upper semi circle to get likeness and that is just what he does in relation to a G individual

The G_I females must be thought to have both the yellow valence curves in Figs 8 and 12 and $B_{I,n}$ females must be thought to have both the green valence curves functioning at the same time (in the same way as we find two different proteins in some heterozygotes for instance by the sickle cell property) This would explain their intermediate reactions We will also expect two different yellow valence curves for the female conductors and for the heterozygotes of the colour blind females

Finally I shall demonstrate in Fig 12 a possible explanation for the sequence of sharpness for the points of pure red pure green pure blue and pure yellow here written in the order of increasing sharpness and ease of fixation In my hypothetical Fig 12 we can measure the angles between the drawn line for the cyanolabe curve and the other curves at the point where the curves are supposed to cancel each other We find the angles 60° 70° 80° and 90° mentioned in the same order From experience of making geometrical constructions at school we all know that it is easiest to find a sharp crossing point between two lines when the angle is large I do not think it is necessary to add anything more after this demonstration

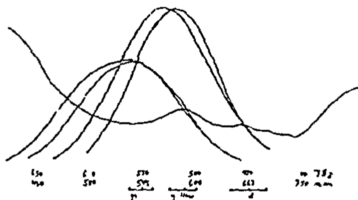


Fig 13 Proposed picture of the absorption spectra for deuteranomal and protanomal males

For deuteranomals and protanomals I presume that the chlorolabe cones are either fewer in number or less effective than for observers with normal colour vision I prefere the first alternative that is the chlorolabe cones are fewer than they are in normal colour vision At the same time the chlolabe cones could be in greater number than those normally occurring The green valence curve would then be lower and the yellow valence curve higher and broader We thus get the picture in Fig 13 in which the two yellow valence curves will cross the cyanolabe curve at shorter wavelengths The green points could then be at the places measured by Rubin (501 6 and 519 7) But we must also suppose that the green valence curves for B and B_1 observers will cross the cyanolabe curve at longer wavelengths because the green valence curves are lower and narrower This explains the earlier mentioned (section III) moving of the blue poitns for the anomalous trichromats and for the female conductors In this way an obser ver s blue point and his green point are moved towards each other and the re gion for the blue green sensation will be shorter

In the discussion on Fig 12 concerning the normals I mentioned that G_1 observeres add more green than do G observers in order to attain the equation the G_2 individuals adding relatively more red As the deuteranomals add much more green and the protanomals add much more red (they are green weak and red weak) we could be led to the confusing conclusion that G_1 and deuteranomal were related, in a family as would be G and protanomal But when we now look at Fig 13 and study the light through the three slits at their middle points (mark 250 on the main screw) we see that there is more yellow stimulation through the green slit and less yellow stimulation through the yellow slit for an anomal observer with a G_1 curve than for an anomal trichromat with a G_2 curve The first must therefore make the light darker through the green slit by mixing

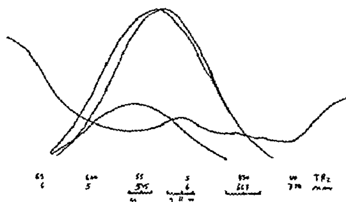


Fig 14 Proposed picture of the absorption spectra for deuteranope and protanope males

more red from the red slit and this is exactly what the protanomal does The other must make the light through the green slit lighter by mixing less red from the red slit and this is what the deuteranomal does The explanation above mentioned of the *differences between normal G_1 and G individuals*, gives an opposite effect for individuals with the normal G_1 and G_2 valence curves This will only give a small moderating effect in the case of the anomals

We can see a stage further in this development in Fig 14 The green valence curve being still even lower the chlorolabe cones even still fewer the yellow valence curve even still higher and broader and the number of chololabe cones even still greater The distance between a point of pure green and a point of pure blue disappears there are only two neutral points where the two yellow valence curves cross the cyanolabe valence curve *the bimodality as before the* G_1 valence curve leading to its neutral point at shorter wavelengths than G valence curve

The illustration in Fig 14 is of course only a rough proposal based upon sparse information Two things could easily be thought to be a little different Firstly there might be a greater difference between the two yellow valence curves Then the left corresponding to the G_1 individual would give a protanope through the green slit (see the horizontal line at the base) much more sensation of yellow than the deuteranope and therefore he would have to make the light through the yellow slit more intense and that is just what he does in relation to a deuteranope Included in the same hypothesis of there being a greater difference between the two curves is that a protanope will receive much less yellow through the red slit than will a deuteranope and thus he must make the light which passes through the yellow slit less intense and that is just what he does in relation to a deuteranope Thus Fig 14 explains the clear difference

between the two types of dichromats An other thing which could easily be possible is that the one drawn green valence curve could pass the cyanolabe curve to the left for the yellow valence curve of the deuteranope (the G curve) This would give him an uncertain neutral point and at the same time give the protanope no green valence at all By removal of his (G_1)curve more to the left one would make the red part of the spectrum less illuminated for him thus giving the impression of a shortening of the red in his spectrum as is usually found in the case of a protanope

In connection with Fig 13 I have supposed that the l in the three middle circles in Fig 7 indicates a mutation producing a new proportion of the chololabe and the chlorolabe cones and making fewer in the case of the last mentioned

In the same way in connection with Fig 14 I assume or postulate that the p in the three lower circles in Fig 7 indicates a mutation producing a further relative increase of the chololabe cones and a reduction of the number of the chlorolabe cones although probably not to zero

q The physiology of colour vision

The effect of admission of coloured light to the eye is received by three different cones The light energy is absorbed and transformd to chemical and electrical energy The rods are also receptors of the light energy but the cones are the most important for colour and for sight acuity

From the cones and rods the effect is lead to the bipolar cells of the retina In the last chapter we saw that we must assume that there are two types of bipolar cells which react in two different ways according to the wavelengths of the present light and for each type we must assume that there are two opposite ways of reaction also dependent of the actual wavelength of the light On the basis of my hypothesis that the stimulus through the cyanolabe cones has an opposing balancing and cancelling effect on the stimuli effect from the two other receptors (the chlorolabe and my chololabe cones) it is also necessary to suppose that a bipolar cell which is connected to a chlorolabe cone is also linked to a cyanolabe cone In the same way the other type of bipolar cell is connected with both a chololabe and a cyanolabe cone This connection of two different cones with one bipolar cell clearly reminds us of the twin cones in fish described by Svaetichin (1956a) a situation which might be called physiological (not anatomical) twin cones In the central part of the visual field where focus is sharpest it is probable that a bipolar cell is connected with only one cyanolabe cone and with one of the two other cones In Hogan Alvardo and Weddell (1971) (H A & W) a midget bipolar cell is referred to as being a monosynaptic cell with a connection to only one ganglion cell and on the other side with one cone (or usually two cones one cyanolabe and one of he other two types of cones) In the peripheral parts of the visual fields there will be more complicated connections between the

cones and the bipolar cells probably partly via the horizontal cells (I refer here also to H A & W 1 c) There are in all around five to six cones on each ganglion cell The numbers are given in H A & W (loc cit) 6 3 mill cones 1 2 *mill axons in the optic nerve Therefore there must be a multi cone connection* with one bipolar cell and thereafter with one ganglion cell and its axon This is natural for the retinal periphery where sight acuity is less than that occurring in the center The cones are in synapsis with the bipolar cells and there will be possibility for two different and opposing transmissions (two different transmission substances) via the excitatory an inhibitory buttons

On the inner side the bipolar cells are in a presynaptic position to the ganglion cells Here we also have excitatory and inhibitory buttons with two different possibilities for transmission The ganglion-cell axons lead the chemical and electrical impulses – and thereby the information of wavelength and thus also of colour – *to the lateral geniculate nucleus (LGN) where there are synapses to the* next link leading to the visual cortical center

The ganglion-cell axons in the optical nerve as described in the last section are of two different types or anyway at least of two types According to the functional difference I called the one type chloro-nerves These lead impulses from the chlorolabe and cyanolabe cones which act in opposing directions The other type I called cholo nerves which lead the impulses from the chlolabe and cyanolabe cones in the same opposing ways

I shall now describe the essentials of how these transformations of the light energy to chemical and electrical energy are known or believed to take place The *three different cones the cyanolabe the chlorolabe and the chololabe* (the last is usually called erythrolabe) will receive a receptor potential when they are hit by an adequate light stimulus This so called receptor potential is a change in the membrane potential of +70 mV from the outside to the inside of the cell when the receptor is at rest The change can be either positive hyperpolarization or negative depolarization It is usually accepted that the receptor potential for the cones is positive i e there will be a hyperpolarization that is, positively charged ions Na^{+} pass out of the cell from the inner end which turns towards the bipolar cell There will also be a flow of Na^{+} on the outside towards the outer end of the cone

The cones are connected to the bipolar cells These are shown (in goldfish) to be of two different types (as *mentioned in last section*) reacting according to the Hering theory of colour vision with graded e fect (graded according to strength of the stimulus) in two different directions hyperpolarization and depolarization dependent on the wavelengths of the light rays Depolarization would mean that positive ions Na^{+} flow into the cell Hyperpolarization would mean that negative ions Cl stream into the cell or that Na^{+} pass to the outer side of the cell membrane The changes occurring in the bipolar cells are also described as re

ceptor potentials I therefore postulate firstly that the one type of bipolar cells is connected to a chololabe cone and the other type with a chlorolabe cone and secondly that the cyanolabe cones are connected with both these types of bipolar cells We must then suppose that the transmission from the cyanolabe cones leads to one of the effects for instance hyperpolarization but I shall not for the present postulate this although I feel that this choice is a reasonable one to make The transmission from the chololabe and chlorolabe cones leads to the other effect and thereby possibly to depolarization

From the bipolar cells the information from the cones will be transferred over the synapses to the ganglion cells in the retina The synapses have two different buttons excitatory and inhibitory and I postulate that the information from the cyanolabe cones goes over the one type of buttons (as above I found it reasonable to think that these are the inhibitory buttons but I will not postulate this) The information from the chololabe and chlorolabe cones passes via the other type of buttons and thus to the cholo nerves and chloro nerves respectively

The events occurring in the ganglion cells and their axons are different from the receptor potentials in the bipolar cells and in the cones which as mentioned are changes in the membrane potential

When transmission occurs via the excitatory buttons Na^+ passes into the ganglion cell At the first Ranvier constriction the K^+ will be forced out this ion being smaller (2 2 Å in diameter) than the more hydrated Na ions (3 2 Å in diameter) (the Cl ion has a diameter of 2 0 Å) The flow of K^+ out of the Ranvier constriction will activate this location and the perforations will dilate so that the larger amount of Na^+ can pass through The inward rush of Na^+ gives a spike which is measured by electrodes placed in or on the axon The Na^+ then passes to the next Ranvier and the process is repeated If the transmission goes via an inhibitory button it will be the Cl that will flow into the ganglion cell But the effect of this will vanish after a few mm It cannot be renewed with the Ranvier constriction process and it just inhibits the spike building It is thought that there is a steady flow of Na^+ into the ganglion cell from the synapsis also in complete darkness It is now said that this inhibitory transmission of Cl will cause a reduction in this constant flow of Na^+ and it is just this information that will reach LGN But this steady flow of Na^+ which also occurs in complete darkness is very weak and it is difficult for me to believe that a small reduction of this flow and spike building can give any real information to the cells in LGN and the cortex But if a real excitatory flow is produced from the light influence on the rods I think the situation can be quite another This flow produced from the total range of the visible spectrum will be perceived as light In this case it is possible to accept that a positive or a negative effect may give the sensation of colour or say information of that particular region of the spectrum which is actually stimulating the receptors in the retina I should suppose that the stimul

us from the rods will be efficient in the same ganglion cell and its axon as the ganglion cell which takes over the effects from the cones Thus we may imagine that the transmission via the excitatory buttons will produce a positive effect to the polarization by the rods whereas the transmission via the inhibitory buttons will produce a negative effect to the depolarization by the rods Thus four different types of information will pass through the axons from the ganglion cells in the retina to LGN 1 A high degree of spike building will occur in the cholo nerves as a result of the summation of the rod depolarization and the depolarization from one of the cone stimulations (I think it is probable that this will be from the chololabe cones but it is not necessary to postulate this) 2 In the same cholo-nerve a low degree of spike building will occur as a result of the depolarization from the rods and the hyperpolarization from the other cone stimulation I have assumed that this hyperpolarization effect will derive from the cyanolabe cone but *it is not necessory to postulate this for the present* But as mentioned above I feel this to be reasonable and I shall in the end of the section indicate some facts which seem to show that this assumption is correct 3 and 4 In the chloro nerves we will have the corresponding two pictures as the effect of the stimulation of rods chlorolabe and cyanolabe cones

These four events in the optic nerve show us exactly the base of the two pair theory Information of blue and yellow goes via the cholo nerves both sets of information *cannot be transmitted at the same time* because they are opposite to each other With the same result the information of green and red is transmitted through the chloro nerves But my picture of the colour perception contains a modification of the theory of Hering On the side of the short wavelengths it is violet that opposes green and yellow balancing green at the blue points (only blue in function therefore we have the sensation of pure blue) and balancing yellow at the green points (only green in function) From the spectrum side of the long wavelengths it is purple that opposes both yellow and green balancing with yellow at the red points (only red in function) and cancelling green at the yellow points (only yellow in function)

It is here convenient to introduce a particular (shortened) terminology I have already introduced cholo nerves i e the axons in the optic nerve which lead *the effect from the chololabe and cyanolabe cones Chloro nerves are the axons* in the optic nerve which lead the effect from the chlorolabe and cyanolabe cones These termes correspond to cyano and cholo bipolar and cyano and chloro bipolar N B[1] The effect from a cyanolabe cone in its deep octave I shall designate porphyro and porphyrolabe (from Greek porphuros purple) I should like to but will not rename the cyanolabe cones to indigolabe (from Greek indikon Indian) because strictly they do not capture the blue but the blue violet) thus also a cyano effect a chloro effect and a cholo effect *meaning the effect* on both bipolar and ganglion cells from the three different types of cones

ceptor potentials I therefore postulate firstly that the one type of bipolar cells is connected to a chololabe cone and the other type with a chlorolabe cone and secondly that the cyanolabe cones are connected with both these types of bipolar cells We must then suppose that the transmission from the cyanolabe cones leads to one of the effects for instance hyperpolarization but I shall not for the present postulate this although I feel that this choice is a reasonable one to make The transmission from the chololabe and chlorolabe cones leads to the other effect and thereby possibly to depolarization

From the bipolar cells the information from the cones will be transferred over the synapses to the ganglion cells in the retina The synapses have two different buttons excitatory and inhibitory and I postulate that the information from the cyanolabe cones goes over the one type of buttons (as above I found it reason able to think that these are the inhibitory buttons but I will not postulate this) The information from the chololabe and chlorolabe cones passes via the other type of buttons and thus to the cholo nerves and chloro nerves respectively

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This cell is described as red on center green off surround For me this illu strates the same pitfall which has produced the name erythrolabe instead of my chololabe The sensitivity curve for the small spot corresponds very clearly to *my yellow valence curve (see Figs 8 and 12)* To me it is obvious that this cell in the LGN is connected in synapsis with a cholo-nerve in the optic nerve and *further backwards to a* corresponding cholo bipolar and a chololabe cone in a region of the retina where the small light spot has stimulated the cones As will *be seen this curve goes from 460 to 640 nm* My yellow valence curve goes from 515–525 to 645–650 nm i e from an individual s green point to his red point In *Fig 12 we see that the real valence curve continues further in both directions* although the effect of yellow is inverted by red purple and violet blue Thus in *my opinion the three points 500 480 and 460 nm are expressions of the cyano* effect in the cholo nerve This cell in the LGN ought therefore to be called *yellow on center in my terminology This means that the information to this cell* in LGN comes through a cholo nerve in the optic nerve

For me it is not necessary to know more but nevertheless I shall try to make my own interpretation of the big spot curve

When such an energy transmission passes through the bipolar end ganglion cells a temporary inhibition is produced in the neighbouring cells The small spot in this case *is located 19° from the fovea Here there are certainly several* cyano and cholo bipolar cells connected to each other by horizontal cells and several ganglion cells are connected via amacrine cells These bipolar and gang lion cells will thus probably transfer excitation to each other Several cyanolabe and several chololabe cones will thus combine their effects in one axon which goes to the LGN

With the big spot the cones that are not stimulated will be inhibited Thus for instance the chloro bipolar and ganglion cells will be inhibited in the region outside the green valence curce

From the neighbouring cells which do not belong to this cholo-nerve will come an inhibitory effect to the stimulated cells and in particular to the cells corresponding to the tested cell in the LGN thus from numerous chloro cells in the surround at 480 to 580 nm and for cyano in chloro in their region of my deep octave that is from porphyro at 600 nm Thereby the reduction in the on response for the tested LGN cell at 600–580–560 and the complete inhibition at 540 nm can be explained Also at 520 500 and 480 nm *(460 not described) there* will be an inhibition from chloro cells of the cells corresponding to the tested cells At the same time *there will be a stimulation of the cyanolabe cones (the* cyano in cholo corresponding to the tested cell) However this effect will not be *transferred to the bipolar cell which is completely inhibited* But when the light stimulus ceases the inhibition will disappear and the cyano in cholo energy is *released causing an off reaction.*

In my opinion this tested cell should be called yellow on centre green (chloro and cyano in chloro) off surround Sventy five such cells have been catalogued

From this interpretation it is evident that the fourth sub type called green off centre after all is of the same kind as the just mentioned first sub-type But the cones the bipolar and ganglion cells corresponding to this LGN cell are not found in the small spot but in the annulus of the big spot Thirteen such cells have been demonstrated

In the same way I feel justified in calling the third sub type green on center yellow (and cyano in cholo) off surround (instead of red off surround)

While this third sub type (in a number of 35) has its corresponding cones in small spot so the second sub type (in a number of 38) called red off centre is of the same kind but with its corresponding cones bipolar and ganglion cells in the annulus of big spot i e in the surround

It is not so important for me that these thoughts particularly about the big spot effects are entirely correct For me it is important that there are at least two types of cells in the LGN Those are the ones responsible for the chloro and cyano (and porphyro) reactions and the ones concerned with the cholo and cyano (and porphyro) reactions i e altogether the cells which correspond exactly to the four events in the optic nerve mentioned in this section just before the study of the LGN cells

A third type (W & H Fig 6A) is described as a fifth sub type The small spot for this cell is located 9° from the fovea The on reaction at the small spot is in complete agreement with my cyano curve (Fig 12) from 420 nm with a maximum at 440–460 and decreasing to 640 nm The three last points 600 620 and 640 correspond to my porphyro in chloro Thus I accept the diagnosis blue on centre (or (not blue but) cyano on centre) but I think that at the big spot there are both chloro and cholo off surround It is a likely supposition that the cell in the LGN is connected with a bipolar cell which is in turn only connected to a cyanoble cone

The on picture of this cell is important for me because it shows that there is in fact a curve of an effect corresponding to my very hypothetical cyano curve in Fig 12 I must admit that I should like to have testings also at 660–680 700 nm which would correspond to my porphyro in cholo The effects here are probably not above threshold About this very hypothetical cyano curve I shall add the following Its possibly less natural part is the region between green point and yellow point I have thought that the cyano curve has its maximal height at 447 nm half the height at 894 nm (porphyro) the third of that height at 596 nm (the musical fifth or quint) and further the fourth fifth and sixth of that height at 670 715 and 745 nm respectively for the musical fourth and major and minor third Thus the curve from 447 nm and the curve from 596 nm will cross each other between the green and yellow points The other secondary curves will also

cross each other so that the picture as a whole will not greatly differ from the unique curve shown in Fig 12 The left shoulder of the porphyro curve probably does not come so much within the range of the visible spectrum However in that case its role will be taken over by the other secondary curves

After these type I cells with their sub-types we come to type II cells designated opponent-colour responses no centre-surround arrangement These 15 cells in the LGN are described as having an on response in one part of the visible spectrum and an off response in an other part at both the small and big spots. Eight of these 15 cells have their neutral point at around 500 nm The first mentioned cell (W & H., Fig 7) is not demonstrated by the measured sensitivities over the entire spectrum and only the reactions at 480 and 580 nm are shown There is a distinct on reaction at 580 nm For the 480 nm reaction I quote A blue spot at 480 nm suppressed the firing throughout the field Nothing is said about any off response The next cell (W & H., Fig 8) has an on reaction at 420–480 nm and an off reaction between (500 nm for big spot) 520 and 640 nm This cell is described at blue on green off' For me it is a blue (cyano) on yellow off although it might be some green off also My explanation is that the tested cell in the LGN is connected to a bipolar cell which is in connection with only one cyanolabe cone which functions from 420 to 480 nm whereas for the rest this bipolar cell is inhibited by chloro at 480-500-520 nm and after that particularly by cholo from 520 to 640 nm When the light stimulus ceases the cyanolabe cone will transfer its light energy to the temporarily inhibited bipolar cell and thus give an off reaction in the LGN The difference between this cell and the cell just mentioned above as a third or fifth sub-type in type I might be explained by supposing that the type I cell has its cyanolabe cone in the periphery of the small spot and thereby resulting in a reduction of the influence of the inhibitory neighbouring cells However the last described cell has its cyanolabe cone near the centre of the small spot, whereby the inhibition is already of decisive influence at the small spot

Altog ther eight such cells are described with cyano on or (in my opinion) cholo on

The seven cells with their neutral point around 600 nm are not accurately described I quote 'They were not thoroughly studied Their neutral point at 600 nm could for me support the idea that they react with on or off at wavelengths corresponding to the deep octave of cyano to 600 and corresponding to the green valence curve from 580 to 480 nm Thus some are porphyro on green off others are green on porphyro off This of course is a very hypothetical interpretation for these cells where only scarce facts are available All the same I shall adhere to a hypothesis that these cells in the LGN of type II are in connection with only one cone respectively cyano or cholo neutral point 500 nm or cyano with the function of porphyro or chloro neutral point 600 nm The two

first are in family with the type I cells in the LGN which receive their inform ation via the cholo nerves The last two are related to the type I cells in the LGN which receive their information via the chloro nerves

In the case of type III cells big spot is not tested only the small spot and annulus for instance small spot with diameter 1 and annulus with an inner dia meter of 1° and an outer diameter of 8° (W & H Fig 12) Fourteen cells react with on response in the small spot and off in the annulus and twenty cells react with an off response in small spot and on in annulus The one described cell is located 25° from the fovea Here there will probably be a considerable integration of horizontal and amacrine cells occurring between the bipolar and ganglion cells and consequently all types of cones can combine their effects via few axons in the optic nerve On-centre cells will have their corresponding bi polar cells and cones in centre On annulus cells in the LGN will have their corresponding bipolar cells and cones in the annulus Thus it is natural to sup pose that we get information here both via cholo-nerves (as type I sub types 1 and 4) and chloro nerves (as type I sub types 2 and 3)

Even if one doubts the correctness of my speculations I still find it alto gether reasonable to suppose that information concerning wavelengths reach four different cells in the LGN corresponding to the four different events in the axons of the optic nerve These are probably + for yellow (a + to the rod ef fect) + for green − for violet to blue (in chloro) and for violet to green (in cholo) and − for purple to red (in cholo) and for purple to yellow (in chloro)

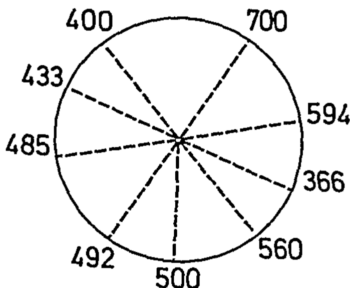


Fig 16 Tschermak s diagram for position of complementary colours in the 'spectrum circle' (From Linksz 1964)

Bringing this section to an end I return to the beginning of the physiology of vision the pigments in the receptors A coloured substance will reflect light with wavelengths corresponding to the colour of the substance For instance a green substance will reflect light with wavelengths between 520 and 550 nm The light energy from other regions will be more or less absorbed more so as the distance increases from the specific region of total reflection until we come to the really complementary region where the light energy is completely absorbed being changed to other forms of energy *In the case of visual purple (rhodopsin)* a colour which is not found in the visual spectrum but is thought to exist in the colour circle gap (see Fig 16) in the infrared say at 1000 nm or in the ultraviolet at 250 nm we may think that the light in the regions of two such wavelengths *will be reflected* Light of wavelengths between 250 and 400 nm and between 1000 and 750 nm we can imagine as only being slightly absorbed The light be tween 1000 and 750 nm arrive at the visual purple with insufficient energy to attain threshold value necessary for the neuro-physiological effect The first sign of sensitivity would be noticed at around 750 nm I suppose that ultraviolet light of 250 nm wavelength will not reach the retina but there could possibly be a subliminal absorption from 370–380–390 nm and we could find the first signs of a physiological effect at 400 nm From both sides, that is from 750 nm and from 400 nm we would have a greater and greater absorption this therefore being the part of the spectrum which is visible until we come to 500 nm the maximum of the scotopic absorption curve This point at 500 nm is thus the real complementary to purple

This description of the absorption of light in the rods agrees with a quotation from Duke Elder (1968) 'The curve correlating the visual threshold with the wavelengths closely corresponds to that defining the bleaching of rhodopsin so that the energy required to bleach the pigment coincides with that required to excite vision This quotation is in correspondance with Granit s findings in 1937

My thoughts are in fact based upon this quotation

From this absorption curve for visual purple we now shall cast a glance at the curves lying at the periphery of Fig 12 the cyano curve and the porhyro curve

The cones responsible for our perception of colour in these peripheral parts of the visual spectrum should as judged by the form of the absorption curves in Fig 12 be expected to produce the sensation of colour also below 400 and above 750 nm This would be so if the absorption of light energy resulted in depolari zation of the bipolar and ganglion cells However if the absorption leads to hy perpolarization in these cells, the sensation of colour will not be produced before the rods are stimulated above the threshold Then the subtraction of the hyper polarization effect of the cyanolabe cones from the depolarization effect of the rods will be perceived as colour

Thus these facts have now lead me to postulate that absorption of light energy

in the cyanolabe cones will produce hyperpolarization in the bipolar and ganglion cells and thus cause a reduction in the depolarization effect of the rods The absorption of light energy in the chlolabe and chlorolabe cones must then be supposed to produce depolarization in these cells

It is not necessary to make specific suppositions concerning the three different pigments in the three types of cones There are a great many examples of isolated pigments but I shall not try to make a selection in this uncertain multitude

However in connection with my speculation about the visual purple (the reflection and absorption of light and the scotopic dominator curve as the picture of the effect of light stimulus to the rods) I shall continue with a similar speculation concerning the effect of stimuli on the cyanolabe cones

From Noller (1951) I have taken his Table 28 pg 618 termed here as Table 8

Wavelengths absorbed (nm)	Colour absorbed	Visual colour yellow green
400–435	violet	yellow green
435–480	blue	yellow
480–490	green blue	orange
490–500	blue green	red
500–560	green	purple
560–580	yellow green	violet
580–595	yellow	blue
595–605	orange	green blue
605–750	red	blue green

Table 8 The relation between absorption and visual colour

Visual purple is able to reflect light in the infrared region (also in ultraviolet when the pigment is directly hit by the light this probably not being the case in the eye) and absorbs light at a decreasing degree on both sides of the maximum at 500 nm to the ends of the visible spectrum (400 and 750 nm) In a similar manner we also find that a yellow green colour (under Visual colour in the Table) absorbs the light in the 400 to 435 nm region

Interpolating in the different regions of wavelengths I find than an absorption maximum at 445 nm (cyano) has its pigment near the yellow in the 582 to 583 nm region An absorption maximum at 890 nm (porphyro) would probably have its pigment close to green at 535 nm Thus the down ward sloping curves from 445 and 890 nm cross each other in the region of 550 to 560 nm and the complete picture would be nearly like the cyanolabe curve in Fig 12 But this cannot be quite correct because in that case we would have two pigments consisting of yellow and green in the cyanolabe cones I could suggest that we had only one pigment (green yellow) or a colour less substance neutral and ineffi

cient which by light of long wavelengths was changed to the green pigment, and by light of short wavelengths was changed to the yellow pigment. It is possible that the cyanolabe cones besides the one substance also contain minimal quantities of the green and yellow to start with (Among the substances found by breaking down of visual purple we have indicator yellow This makes it possible to assume a coloured substance – all these pigments contain similar chromophore groups – which by small changes in pH could change to other colours)

In the section r I have some results from the electroretinography which could indicate in the direction of this audacious hypothesis

r Electroencephalography and electroretinography

My last experiments were made with the intention of seeing whether an application to the retina of light stimuli of different wavelengths would give different electroencephalographic answers in the visual cortex

An electrode for placement on the centre of the visual cortex was placed 5 cm above the inion (external occipital tuber) and 5 cm to the side of the median line The reference electrode was placed 5 cm above the first

By this arrangement a short flash (0 01 msec) of light to the eyes will in the usual electroencephalographic picture of waves be completely undetectable However by means of the apparatus which I used it was possible to send 150–200 flashes after each other (2–3 seconds between each flash) each of the flashes starting a data machine which at 400 points per second was able to take up pictures of the waves (remembered (!) them) so as to give the final sum of 150–200 flashes The other uninteresting waves in greater or lesser degree cancelled each other out so that the sum as calculated by the computer was able to give a clearer and enlarged picture of the specific waves which were under investigation

I u ed filters produced by Jenaer Glaswerk Schott & Gen Mainz The filters were almost monochromatic and enabled the passage of a sharp region of colours and practically nothing greater than ± 10–15 nm outside of the maximum point I used nine pairs of filters placed in diver spectacles Four near the pure colours three between them blue green green yellow and orange and two for the most peripheral parts of the visible spectrum The producer give the maxima of the transmitted light at the following nine points 451 nm 482 (blue) 500 517 (green) 552 582 (yellow) 615 662 (near red) and 727 nm

The first result is presented in Fig 17 where the filter giving 451 nm was used Very near 50 msec after the flash we see the start of a wave which is some times repeated every 90 msec Only the first wave will be the direct answer to the flash. The following flashes are explained as being a self inhibiting situation occurring through small nerve fibres The inhibition is released after the wave has passed

and the arrival of the ordinary steady spikes to the synapsis start the next wave which usually is greater than the actual answer

None of the following testings – on observers with normal colour vision (with genotypes for males B_1G_1 B_1G B G_1 and B_2G_2) and the different types of colour blindness – gave similar relatively regular pictures In the first B_1G_1 observed (Fig 17) the greatest similarity was found using the 727 nm filter Note the small secondary wave at the place for 100 msec which could also be found in some of the other pictures But the connection of the different filters with their different permeated wavelengths of the light was not clear to me My main impression was that 'something' began to occur at 50 msec as shown in Fig 17

However I must indicate two causes of complexity Firstly the nerve reactions in the region of the cortex do not stop at the first synapses to the cells of the cortex where the axons from the LGN are presynaptic In a region around the centre there will be further transmissions to other ganglion cells There are hundreds of these in this miraculous system which enables our conscious perception of that which has started in retina It is impossible to know as to what degree the electroencephalogram will be affected

Secondly I used in these testings a great circular plane of 10 cm diameter for the flashes With a distance from the eyes of 70 cm this would mean an angle of 8–10° Thus a great and probably variable area of retina was stimulated from flash to flash I therefore guessed that the main effect which could be discovered in the EEG might come from the rods there being only small and undeterminable part from the cones

All these testings performed on around 20 observers thus seemed to be in vain

However when I had made the investigations (described below) with the electroretinograms (ERG) it was possible to study the EEG taking a different point of view It looks like one can summarize the pictures for the 451 nm at the 727 nm filters thus

451 up at 0 7 cm (35 msec) to a maximum at 1.3 cm repetition of max 90 msec
727 up at 0 8 cm (40 msec) to a maximum at 1.5 cm repetition of max 100 msec

It is possible that the differences in the figures could be an expression for a weaker or stronger (?) or an other stimulus effect in the cyanolabe cones when this stimulus came from the long wavelengths than when they came from their



Fig 17 Electroencephalogram from the visual cortex

typical region of short wavelengths Further I lay stress upon the wave around 2 cm (100 msec) mentioned above With the experience from ERG I would be inclined to ascribe this to a special rod effect which was delayed in relation to the cone effect, in the same way as noted for the b and a wave in the ERG

For the 517 nm filter (green) and the 582 nm filter (yellow) I can make these common remarks There is a wave maximum between 2 8 and 3.3 cm with a repetition occurring every 100 msec I could say that there is an invisible posi tive wave from 0 8 cm (40 msec) made visible by the downward sloping wave between 1.3 and 1 9 cm This invisible upward turning wave should be ac cording to my speculations in the section q the result of the summation of the rod effect and chloro or cholo effect respectively If there is as mentioned in section q special information coming from the rods via particular optic nerve fibres besides the chloro-nerves and cholo nerves the general effect in the regions of these (green and yellow') wavelengths could be such that the particular chloro and cholo effect would be very small or lacking in this summation (We have seen in Fig 17 that also for violet (451 nm) the first wave at 0 8 or 0 7 is small) For the two filters (517 and 582 nm) there is also a clear positive wave at around 2 cm (100 msec), above supposed to be a delayed rod effect The two filters transmit light mainly with the chloro and the cholo effect respectively Both filters transmit light at around the green point and around the yellow point, and thus there might be complications arising from the blue and yellow on both sides of the observer s green point and from the green and orange on both sides of the observer s yellow point All this explains the difficulty of deriving any meaning from the different wave patterns of the EEG

In the case of the filters 482 and 662 nm intended to cover the blue points and the red points the above mentioned small complications will become the main complications arising from the lilac and green around the observer s blue point and from the yellow and dark red (purple) around the observer s red point. Therefore I shall abstain from analysis of the details of these wave pictures

Probably I should not lay too much stress upon the differences derived from the different filters Altogether they may have principally alike pictures. The first wave rises at 0 8 cm the next (greater but only indirectly produced from the receptors) rises at 2 8 cm with 2 cm repeating distances For all of them there might be a common upward going tendency a small positive (rod depen dent?) wave at around 2 cm But perhaps the differences between the 451 and 727 nm filters could explain why we have two different perceptions although my hypothesis states that in both cases we have the stimulus effects from the cyanolabe cones Perhaps the chemical and electrical effect is not exactly the same but only similar the effect at 727 nm being smaller and more sluggish than the effect from the high energy light through the 451 nm filter However in Fig 12 there lies an other probably more important difference At 451 nm it is the

green valence curve that starts the diminishing of the cyano effect At 727 nm its is the yellow valence curve that has this function Therefore at 451 nm more of the cyano will pass through the cholo nerve and at 727 nm more will pass via the chloro nerve

For the electroretinography (ERG) I used a contact lens annular in form with a central lens transmitting light and dispersing it diffusely over the retina The electrode on the inside of the contact lens against the cornea points to the inner side of the retina in the direction of the ganglion cells to the pigment epithelium whereas the reference electrode is placed upon the other side of the lens against the inside of the eyelid

I used here the same short (0 01 msec) flashes I did in the cases of the EEG a series of 50 of them being summed up in the data machine

The first effect of light stimulus is the movement of positive electricity (Na^+) upwards in the receptor against the synapses to the bipolar cells A so called early positive potential with latency time of 0 025 msec based on movements of electrical charges (Duke Elder 1968 pg 502) is explained by this Na^+ move ment This early potential is difficult to discover and is not found in my pictures But then Na^+ also moves on the outer side of the receptor in the other direction against the outer end of the receptor This is a situation of hyperpolarization i e a difference between the outside and inside of the receptor membrane greater than the 70 mV at receptors when not stimulated This is the cause of the later potential or the negative a wave wih a latency of 3 msec This a wave is the first part of the retinograms as seen in my testings In good retinograms one can find its bipartite nature (again Duke Elder, 1968 pg 504) Fig 18 the early pho topic i e from the cones and a later scotopic i e dependent on rods both as minima Fig 18a and b in the downward sloping wave

The b wave is (Duke Elder 1968 pg 505) the most important in the electro retinogram undoubtedly related to optic nerve discharges with origin somewhere between the receptor and the ganglion cells Also this positive wave might show an early photopic and a later scotopic maximum Fig 18c and d To me this is explained (as described in the section q) by the passage of Na^+ across the synapses to the bipolar cells the diffusion in the bipolar cells and passage via the synapses to the ganglion cells

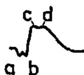


Fig 18 Picture of an a wave and a b wave (A part of Fig 178 s 505 Duke Elder 1968)

According to my postulates in section q all this will occur as the stimulus effect arrives from the rods, chololabe and chlorolabe cones But as the stimulus effect arrives from the cyanolabe cones also in the porphyrolabe region we would expect a Cl passage through the synapses instead of Na^+ passage thus causing a negative b wave (!) probably as a continuation of the a wave

A later c wave in the ERG is (Duke Elder 1968 pg 507) unrelated to the visual process composite in origin from pupillary musculature and pigment epithelium in the retina

The question I made with my testings was just to see if we can find such an un-orthodox (heretical) negative b wave

If we now study the pictures of my two first electroretinograms in Figs 19 and 20 for the 451 nm filter (near the maximum for the cyanolabe cone) respectively for the 552 nm filter (near the crossing of the green and yellow valence curves (see Fig 12) where the sum of the cholo and chloro effect probably is greatest, at the photopic maximum) I may thus make the following speculations

The 552 nm picture is as I see it like most of the electroretinograms which I have seen reproduced The a wave sinks down to a minimum at 0 55 cm (27 5 msec) and the b wave reaches a maximum at 1 3 cm (65 msec)



Fig 19

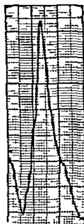


Fig 20



Fig 21



Fig 22

Figs 19–22 Electroretinograms using the filters 451 552 662 and 482 respectively

The 451 nm picture shows a downward sloping wave in three steps and has its minimum at 0 75 cm (37 5 msec) It seems reasonable to assume that the first slope downwards represents the first part of the a wave The levelling off could be an expression for the building of the yellow pigment from the neutral sub stance (as mentioned in section q) whereas the downward slope was caused by the yellow pigment already being there The second step continues as for the rest of the a wave possibly indicating in the direction of 0 55 cm 27 5 msec But then we have the third step which could be the heretical negative b wave down to 0 75 cm 37 5 msec We would have expected that the minimum of the nega tive b wave would be at 1 3 cm 65 msec (as the positive maximum for the b wave by the 552 nm filter) However it is seemingly interrupted by a positive b wave which reaches maximum not at 65 msec but at 80-85 msec This positive b-wave could be explained as being a delayed b-wave dependent upon the stimuli effect from the rods (delayed as mentioned by Fig 18) as this rod effect will dominate the picture in lieu of the weaker effect from the cyanolabe cones

I must admit that it is daring to conclude so much from this picture But when we study the ERG for the 662 nm filter which is in the red i e at longer wave lengths than the subject s red point (at 645 nm) we find a similar picture the stepwise negative decreasing to 0 75 cm 37 5 msec However the b wave reaches already a maximum at 1 3–1 5 cm 0 65–0 75 msec being more like a typical b-wave maximum i e as for the 552 nm filter at 0 65 msec The explan ation could be that yellow (in the orange) has passed the 662 nm filter This will thus dominate the picture here and give in addition to the negative b wave a positive b wave (from the chlololabe cone) in interference with the weaker hereti cal negative b-wave

The 482 nm filter should allow light of wavelengths around the blue points to pass through but the filter will obviously also be passed by some of the green and this stimulus effect from the chlorolabe cone will predominate over the weaker effects from the cyanolabe cones Thus the picture is altogether similar to the picture obtained with the 552 nm filter i e the ordinary a wave and b wave with minimum and maximum as for the 552 nm filter The amplitude for the b wave is however smaller with the 482 nm filter than with the 552 nm fil ter which is quite natural

We see from all this that one can only hope to find the postulated negative b wave when we use efficient and practically monochromatic filters in violet and dark red Usually one will therefore always find the same picture in all parts of the spectrum only the amplitudes vary according to the different sensitivenes for the different regions of the spectrum with maximum sensitivity around 550 nm the photopic maximum

I twice also tried the 727 nm filter the second test with another contact lens with the reference electrode on the glabella but no clear pictures of waves in the

retinogram were found The observer in the last case clearly perceived the red colour but it was a very dark red and it will be natural to suppose that the certainly existing potential difference between the two sides of the retina will not be measurable between the relatively very distant electrodes

But altogether when we particularly note the electroretinograms by the use of the three filters 451 552 and 662 nm the main conclusion might be that there are in fact negative b waves in the violet and purple, indicating the occurrence of hyperpolarization in the bipolar and ganglion cells

REFERENCES

Adam A The linkage between protan and deutan loci The Am J Hum Genet. 22 691 1970

Duke Elder S System of ophthalmology Vol VII London 1962
— System of ophthalmology Vol IV London 1968

Granit R Absorption curve for visual purple and the visual response of the frog s eye. Nature 140 972 1937
— The red receptor of Testudo Acta physiol Scand 1 386 1941a
— Isolation of colour sensitive elements in a mammalian retina. Ibid 2 93 1941b
— A relation between rod and cone substances based on scotopic and photopic spectra of Cyprina Tinca Anguilla and Testudo Ibid 2 334 1941c.
— Colour receptors of the frog s retina Ibid 3 137 1941d
— Spectral properties of the visual receptor elements of the guinea pig Ibid 3 318 1942a.
— The photopic spectrum of the pigeon Ibid. 4 118 1942b
— Red and green receptors in the retina of the Tropidonotus Ibid 5 108 1943a
— The spectral properties of the visual receptors of the cat Ibid 5 219 1943b
— Sensory mechanisms of the retina London Oxf Univ Press 1947
— Receptors and sensory perception Yale Univ Press 1955
— & G Svaetichin Principles and technique of the electrophysiological analysis of colour perception with the aid of microelectrodes Upsala Lakaref forh 65 161 1939

Hogan Alvardo & Weddell Histology of the human eye Philad. Lond Toronto 1971

Kalmus H. & M Case The distribution of the spectral locus of Unique green in samples of normal trichromats Ann Human Genet 35 369 1972

Krill A. E., V G Smith & J P Pokorny Similarities between congenital tritan defects and dominant optic nerve atrophy Coincidence or identity J opt soc Amer 10 457 1970
— Further studies supporting the identity of congenital tritanopia and hereditary dominant optic atrophy Invest. ophth 10 457 1971

Kollner H Die Storungen des Farbensinnes Berlin 1912

Linksz, A An essay on color vision and clinical color vision tests New York and London 1964
— & G Waaler Naming of groups with normal colour vision Nature 218 687 1968

Marks W B Difference spectra of the visual pigments in single goldfish cones (Thesis) John Hopkins Univ Baltimore 1963
— W H Dobelle & E. F MacNichol jr Visual pigments of single primate cones. Science 141 1181 1964

Monod J Le hasard et la nécessité Essay sur la philosophie naturelle de la biologie moderne Editions de Seuil 1970

Morgan T H Die stofflichen Grundlagen der Vererbung (Deutsche Ausgabe von H. Nachtsheim) Berlin 1921

Noller C R. Chemistry of organic compounds Philadelphia & London 1951

Richards W Differences between color normals J optic soc Amer 57 1047 1967

Rubin M L. Spectral hue loci of normal and anomalous trichromates Amer J ophth 52 166 1961

Rushton W A H Kinetics of cone pigments measured objectively on the living human fovea Ann N Y acad sc. 74 291 1958
— Visual pigments in man Scientific American 207 Nov 120 1962

Schiotz I Colour blind females The inheritance of colour blindness Brit J ophth 4 343 & 393 1920

Svaetichin G Special response curves from single cones Acta physiol scand Suppl 134 17 1956a
— The cone function related to the activity of retinal neurones Ibid 67 1956b
— Aspects on human photoreceptor mechanisms Ibid 93 1956c
— & E F MacNichol jr Retinal mechanisms for chromatic and achromatic vision Ann N Y Acad sc 74 385 1958

De Valois R L. Color vision mechanisms in the monkey J gen physiol 43 (6) Part II 115 1960

Wiesel T H & D H Hubel Spatial and chromatic interactions in the lateral geniculate body of the Rhesus monkey J neurophys 29 1115 1966

Waaler G H M Über die Erblichkeitsverhaltnisse der verschiedenen Arten von angeborener Rotgrunblindheit Z. f indukt Abst u Vererb lehre 45 279–333 1927
— Über die Erbl etc Acta ophth. V 309–345 1927
— The heredity of normal and defective colour vision Avh D norske Vidensk Akad I No 9 1967
— New facts in the genetics of colour vision besides ideas of the colour perception Avh D norske Vidensk Akad I No 11 1968
— The heredity of normal and defective colour vision Acta ophth 46 33 1968b
— Studies in colour vision Avh D norske Vidensk Akad I No 12 1969
— Further investigations on different hereditary colour vision properties. Avh D norske Vidensk Akad I No 14 1973

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ACTA OPHTHALMOLOGICA
SUPPLEMENTUM 123

Congressus XXI ophthalmicorum septentrionalium

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Congressus XXI ophthal
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Turku Finland 1973

Vammala 1974 Vammalan Kirjapaino Oy

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13–16 June 1973

Congressus XXI ophthalmicorum septentrionalium

OFFICIAL TRANSACTIONS

EDITED BY
A OKSALA AND S POHJOLA

Wednesday June 13th

Reception

Official opening of the exhibition at the University of Turku Finland

Thursday June 14th

Opening address by the President of the Congress Professor Arvo Oksala 9

Aqueous humour dynamics

Chairman Professor Gunnar von Bahr (Uppsala)

Barany E Outward-directed transport systems in the eye and choroid plexus 12
Linner E Aqueous humour dynamics in ocular hypertension 14
Svedbergh B Ultrastructure of the chamber angle after a short period of high intraocular pressure 15
Palkama A Uusitalo R & Stjernschantz J Some aspects of nervous control of aqueous humour dynamics in the rabbit eye 17
Pechardt L Palkama A & Uusitalo R Electron microscopical studies of the acetylcholinesterase-positive and -negative nerve fibres in the ciliary body of the albino rat 21

Chairman Professor Ernst Bárany (Uppsala)

Saari M Morphological basis of diffusion through the iris vessels in the dynamics of the aqueous humour 26

Sjostrand J & Karlsson J O Axonal transport in the retinal ganglion cells of the rabbit under different experimental conditions 31

Ruusuvaara P & Palkama A Effect of short term increased intraocular pressure on the fine structure of the retina 41

Tarkkanen A & Laatikainen L Dose response analysis of 0 1 % 0 5 % 1 0 % and 2 0 % epinephrine in chronic open-angle glaucoma 47

Valle O Effect of cyclopentolate on the aqueous dynamics in incipient or suspected open angle glaucoma 52

Afternoon session

Chairman Professor Poul Brændstrup (Copenhagen)

Uusitalo R Stjernschantz J & Palkama A Studies on the ultrastructure of the blood-aqueous barrier in the rabbit 61

Stjernschantz J Palkama A Uusitalo R & Renkonen O V Aspects of the blood aqueous barrier with special reference to the penetration of antibiotics 69

Salminen L Effect of paracentesis on ocular antibiotic concentration 75

Saari M Observations on the structural arrangement of the somatic sensory innervation in the iris of mammals 77

Seland J H The ultrastructure of the aged human lens capsule 81

Chairman Professor Gosta Karpe (Stockholm)

Palva M & Palkama A Sodium potassium-activated adenosine triphosphatase (NaK-ATPase) activity in the rat lens 82

Tervo T & Palkama A Histochemical findings on sodium-potassium activated adenosine triphosphatase (NaK-ATPase) activity in the cornea 88

Perasalo R Rechardt L & Palkama A Chloroquine-induced ultrastructural changes in the pigment epithelium of the albino rat 94
Perasalo R Rechardt L & Palkama A Effect of chloroquine on acid phosphatase activity in the pigment epithelium of the retina of albino and pigmented rats 99

Friday June 15th

Intraocular tumours

Chairman Professor Thore Lie Thomassen (Oslo)

Horven I Retinoblastoma in Norway 103
Warburg M Genetic counselling in retinoblastoma 110
Jerndal T & Tengroth B Treatment of retinoblastoma 116

Chairman Professor Eilif Gregersen (Copenhagen)

Jensen O A Egeberg J & Edmund J Effect on growth and structure of transplantable malignant melanomas of the Syrian golden hamster (Mesocricetus auratus) by depletion of phenylalanine and tyrosine in the diet and by inhibition of tyrosinase 120
Vannas S Raitta C & Tarkkanen A Neurilemmoma of the choroid in Recklinghausen s disease 126
Helve J & Nieminen H Simultaneous bilateral fluorescein angiography of the anterior eye 134

Chairman Professor Erik Linner (Umea)

Oksala A Ultrasonic diagnosis in melanoma and retinoblastoma 136
Aasved H & Seim V Chemotherapy in intraocular metastasis from carcinoma of the breast 142
Nordman E & Nordman L E O Radiation treatment of intraocular cancer metastases 147
Tarkkanen A & Merenmies I Basal cell carcinoma of the eyelids 152

Afternoon session

Pediatric ophthalmology

Chairman Professor Hans-Walther Larsen (Copenhagen)

Odland M Causes of blindness and severe vision impairment in children A regional investigation 153

Krause U & Rantakallio P Paediatric ophthalmology in Northern Finland — a population investigation 154

Hvidberg Hansen J Larsen F E & Kleener J Dyskeratotic marginal keratoconjunctivitis in hereditary periodontopathy and hyperkeratosis 157

Raitta C & Perheentupa J Mulibrey nanism an inherited dysmorphic syndrome with characteristic ocular findings 162

Chairman Professor Gote Österlind (Malmo)

Vannas A & Nanto V Corneal dystrophy associated with a variant of mucopolysaccharidosis 172

Raitta C & Santavuori P Neuronal ceroid lipofuscinosis of early onset 173

Takki K & Simell, O Gyrate atrophy of the choroid and retina with defective ornithine metabolism 174

Møller P M Goniotomy in congenital glaucoma 175

Chairman Professor Sven-Erik Nilsson (Linkoping)

Davanger M & Spetalen S Congenital cataract Material 178

Ehlers N & Schønheyder F Concentration of amino acids in aqueous humour and plasma in congenital cataract or dislocation of the lens 179

Fledelius H Influence of low birth weight on the visual acuity in school-age 190

Merenmies L & Tarkkanen A Chronic cyclitis in children 191

Erkkila H Drusen of the optic disk on children 197

Saturday June 16th

Free papers

Chairman Professor Poul Martin Møller (Odense)

Goldschmidt E & Løchte J Treatment of a case of sympathetic ophthalmia 198

Nikoskelainen E & Riekkinen P Retrospective study of 117 patients with optic neuritis 202

Ahvonen P & Dickhoff K Uveitis episcleritis and conjuctivitis associated with Yersinia infection 209

Wold E Opetative Behandlung von rezidivierenden Fehlstellungen der Lider mit glycerinkonservierter Sklera 213

Stenkula S Kock E Rydberg M & Tornquist R Surgical repair of scleral defects 220

Chairman Professor Arvid Anseth (Tromsø)

Krogh E Electro oculography A clinical normal case series 221

Wachtmeister L Wavelet-ERG during light- and dark-adaptation 222

Simonsen S E Prognostic value of ERG (oscillatory potential) in juvenile diabetics 223

Voipio H Arrestovi ography a method for objective assessment of visual acuity 225

Chairman Professor Arvo Oksala (Turku)

Gregersen E Pontoppidan M & Rindziunski E Optic and drug penalization and favouring in the treatment of squint amblyopia 228

Holm K Corneal reflection of a straight line and ophthalmometry in normal people and in asymptomatic relatives of patients with keratoconus 229

Rydberg M & Wold E A simple modification of the Tudor Thomas eye piece stand 231

Rysa P & Sarvaranta J Thermography of the eye during cold stress 234

Liesmaa M & Vannas A Hydrophilic contact lenses — indications and follow-up 240
Liesmaa M Driver s visual acuity in relation to his driving 241

Film program

Vannas S Mantyla P & Vannas A Trabecular surgery of open-angle glaucoma Remarks on microcirculation 242
Vannas S Raitta C & Mantyla P Combined iridocyclectomy and trabeculectomy with sclerectomy for tension raising tumour of anterior uvea 243

GENERAL MEETING

Report on N O L R 244
Congressus XXII Ophthalmicorum Septentrionalium 244
Nordic courses in Ophthalmology 244
Report on Acta Ophthalmologica 244
Presentation of the K K K Lundsgaard Medal 245
Members of the Meeting 246

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13–16 June 1973

OPENING SPEECH

The tradition of Meetings of Nordic Ophthalmologists dates back to as early as 1900 in Stockholm Initially attempts were made to arrange a meeting every third or fourth year but both world wars caused an interruption of almost 10 years since 1963 however meetings have been held every second year This is the third time that the Meeting of Nordic Ophthalmologists has been held outside the capital cities in 1954 the Nordic Congress was held in Gothenburg and in 1969 in Bergen

Turku the oldest town in Finland was founded in its present situation almost 750 years ago and was the capital of Finland until 1812 After the Great Fire the University was moved to Helsinki in 1828 and the city was left without an institution for higher academic education for almost 100 years The present University of Turku which is now almost completely state subsidized and will probably shortly become a state university was founded in 1920 its Medical School was started in 1943

The present Meeting of Opthalmologists in Turku has aroused great interest We have about 250 active participants and 150 non-active ones including relatives etc Before the Second World War considerably fewer participants attended these meetings usually fewer than a hundred. The previous meeting in Finland at Helsinki in 1963 attracted some 150 active participants Many papers have been submitted to this congress that is about 65 Until 1954 the number of papers submitted remained

around 30 to 35 but there are obvious reasons for the subsequent increase in the number of participants and papers The total of ophthalmologists has grown in all Nordic countries and research projects have become more extensive and profound The growth of these meetings has also compelled the organizers to set various restrictions usually owing to shortage of time and funds We have had to restrict the time allotted to talks and discussions as well as the length of papers to be printed These restrictions have however made it possible to reserve some time even if very little for personal contacts and some social events with our friends and companions

From the very beginning the Meetings of Nordic Ophthalmologists have had certain goals which can be attained we hope quite easily by us who live in the Nordic countries The centuries-old and common Nordic cultural tradition has made us all think and act alike and thus the Meetings of Nordic Ophthalmologists have represented a small link in the long chain of this Nordic cooperation in various fields One of the main goals has naturally been the presentation of scientific achievements broadening research and above all improvement in the quality of the latter Nordic congresses are more suitable for this purpose than mere national meetings of ophthalmologists On the other hand so far the Nordic Meetings have managed to remain events on a less gigantic scale than large international meetings where very little is left of a cooperative spirit among ophthalmologists and where also the criticism of scientific work has suffered And last but not least there is another important goal In his paper presented at Gothenburg in 1954 K O Granstrom said that the invitation to the 1900 meeting had emphasized that the main aim of the meeting should be personal contacts and not the presentation of scientific work As a matter of fact nothing was published after this meeting only a small summary by Gullstrand in *Klinische Monatsblatter fur Augenheilkunde* To quote Granstrom further the only participant of the 1911 Helsinki meeting who was still alive (and 92 years old) at the time of the 1954 meeting Gustav Ahlstrom said that the 1911 Helsinki meeting had never been surpassed in the amount of champagne consumed And one more quotation from the 1928 Oslo meeting »One can always read the papers afterwards but the dinners and the wines » These spirited reactions well describe the relaxed atmosphere and good temper which have always prevailed in both the scientific and social occasions The organizing committee of the present meeting in Turku hopes that we may be able to follow this tradition here as well

On behalf of the organizing committee I wish all participants and their companions heartily welcome at this XXI Meeting of Nordic Ophthalmologists here in Turku

Since the 1971 meeting in Reykjavik three of our colleagues have died Sverre Kolstad Karl-Henrik Sjoström and Herbert Wolff from Sweden I suggest that we honour their dear memory with a moment s silence

Professor Arvo Oksala
President of the Meeting

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13—16 June 1973

Department of Pharmacology (Head Professor E Bárany)
University of Uppsala Sweden

OUTWARD DIRECTED TRANSPORT SYSTEMS IN THE EYE AND CHOROID PLEXUS

Protection of the eye against circulating toxic substances and drugs

BY

ERNST BÁRANY

When incubated in vitro in a potassium-rich medium the anterior uvea choroid plexus and kidney cortex of rabbits actively accumulate o-iodohippurate ^{131}I iodipamide-^{1} I cholate-^{14}C and glycocholate-^{14}C

Excess hippurate can suppress the uptake of o iodohippurate-^{131}I completely but leaves an appreciable hippurate insensitive fraction of iodipamide-^{125}I uptake (Barany 1973) Excess iodipamide (unlabelled) can *suppress the uptake of o-iodohippurate and labelled iodipamide completely* but leaves about 40 % of cholate and 10 % of glycocholate uptake Hence at least three distinct transport systems are involved

1) o-iodohippurate accumulation 2) hippurate insensitive iodipamide accumulation and 3) iodipamide insensitive bile acid accumulation These represent at least three transport systems which are most probably outwardly directed These will affect the penetration and intraocular concentration of drugs and metabolites

Reference

Barany E (197?) Inhibition by hippurate and probenecid of in vitro uptake of iodipamide and o-Iodohippurate A composite uptake system for iodipamide in choroid plexus kidney cortex and anterior uvea of several species *Acta physiol scand 86* 12—2?

To be published in full in Acta physiol scand

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13–16 June 1973

Department of Ophthalmology
University of Umeå Sweden

AQUEOUS HUMOUR DYNAMICS IN OCULAR HYPERTENSION

BY

ERIK LINNÉR

A total of 92 patients with moderate ocular hypertension were kept under clinical observation for ten years without antiglaucoma therapy (group I) There was no evidence of progressive disc cupping or field defects For comparison a group of 90 individuals was chosen at random from the case records of the department of surgery at Skovde hospital (group III)

The results reported here were based on measurements of the intraocular pressure made in a recumbent position with a hand held applanation tonometer and regular tonography performed with a standardized electronic Schiotz tonometer The analysis was limited to the right eye which was examined first

The intraocular pressure was about 6 mm Hg higher in group I than in group III and the facility of outflow about 0 07 μl/mm Hg/min lower The rate of aqueous flow was calculated assuming the episcleral venous pressure to be 10 mm Hg In group I the flow value was 2 54 μl/min and in group III 1 79 μl/min — a significant difference Using a tonographic method when the intraocular pressure was kept constant Thorburn found no significant difference in the facility of outflow between 30 individuals from each of these two groups Thus the difference in flow values between group I and group III was more considerable

The evidence of this study supports an increased rate of aqueous flow as the main reason for ocular hypertension in group I Additional factors such as the episcleral venous pressure and pseudofacility might also play a part and further studies are planned

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13–16 June 1973

The University Eye Clinic Uppsala Sweden

ULTRASTRUCTURE OF THE CHAMBER ANGLE AFTER A SHORT PERIOD OF HIGH INTRAOCULAR PRESSURE

BY

B SVEDBERGH

When intraocular pressure (IOP) is maintained at 33—44 mm Hg for 3—7 hours by perfusion in vervet monkeys the total facility increases about 3-fold and morphological changes occur the endothelial cells of the trabecular meshwork swell and »blebs» are observed In Schlemm s canal the inner wall endothelium as well as the adjacent endothelial meshwork are partly washed away The corneal endothelium shows roughness of its surface pyknosis exkaryocytosis mitotic activity and loss of whole cells

After 3 days morphology IOP and facility return to normal

Discussion

O A Jensen How about fixation artefacts?

Answer The control eyes maintained at spontaneuos IOP levels showed no fixation artefacts However the eyes maintained at high IOP are probably more sensitive to artefactual influences

B Ehinger Have you observed any morphological changes peripheral to Schlemm s canal?

Answer Nothing obvious except a slight roughness of cell surface of the outer wall endothelium

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XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13–16 June 1973

Department of Anatomy (Head Professor O Eranko)
University of Helsinki Finland

SOME ASPECTS ON NERVOUS CONTROL OF AQUEOUS HUMOUR DYNAMICS IN THE RABBIT EYE

BY

ARTO PALKAMA RISTO UUSITALO and JOHAN STJERNSCHANTZ

Intraocular pressure (IOP) is regulated mainly by three factors the rate of aqueous inflow (F) facility of aqueous outflow (C) and episcleral pressure (Pv) It has been suggested that some ions are actively transported (secreted) from the plasma into the eye Furthermore the eye is richly innervated by autonomic and other nerves which have been assumed to take some part in this active secretion of ions into the eye and thus also in aqueous humour dynamics

The present paper aims to describe some of our research group s findings on the correlation between the aqueous humour dynamics and the function of the nerves supplying the eye

Material and methods

Altogether we have used about 300 rabbits weighing between 1 and 3 kg Intra ocular pressure rate of inflow and outflow facility were measured manometrically according to a modified technique described by Sears and Barany (1960) Aqueous inflow was calculated from changes in IOP during saline perfusion according to the *formula*

$$F = \frac{\Delta F}{\Delta P}(Po - Pv)$$

(ΔF = rate of infusion in μl/min ΔP = increase in IOP PO = primary IOP and Pv = episcleral venous pressure = 9 mmHg) Arterial blood pressure was recorded manometrically as well

Sympathetic denervation or stimulation was performed by dissecting or stimulating (pulse frequency = 13/sec duration = 2 5 m sec and current output = 0 6 mA) the superior cervical ganglion (Fig 1) Ocular dynamics were analyzed 5 days after the operation

Parasympathetic and ophthalmic nerve denervations were performed stereo tactically by intracranial electrical coagulation (Fig 1) Ocular dynamics were analyzed 5 (7) days after the operation

Parasympathetic nerves (Fig 1) were stimulated by using a bipolar teflon coated steel electrode and unidirectional square wave (pulse frequency = 44/sec duration = 0 8 m sec and current output = 2—3 mA) impulses

Biochemical sodium potassium activated adenosine triphosphatase (NaK ATPase) activity was measured by using a kinetic enzymatic technique

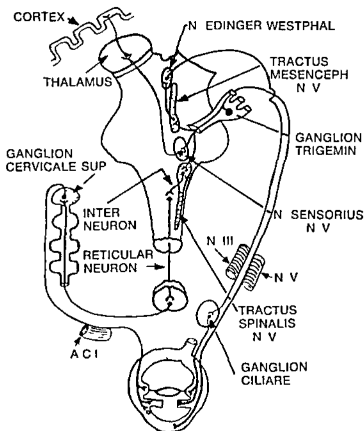


Fig 1
The ocular nerves and their connections with regard to the nervous control of intraocular pressure

Statistical evaluations were made either with matched pair t test or with t test between two means

A more detailed description of all the techniques and references may be found in Uusitalo (1972)

Results

The results obtained are presented in Fig 2 The significant changes may be summarized as follows

1 Sympathetic stimulation decreases IOP
2 *At the same time as IOP is decreased during the sympathetic* stimulation the rate of inflow and the outflow facility is also decreased
3 Parasympathetic stimulation increases IOP
4 Parasympathetic denervation decreases IOP
5 Simultaneously with the decreased IOP 5 days after parasympathetic denervation the ciliary body-iris NaK-ATPase is decreased
6 Ophthalmic nerve denervation increases the facility of outflow
7 Arterial blood pressure remained unchanged during the stimulation

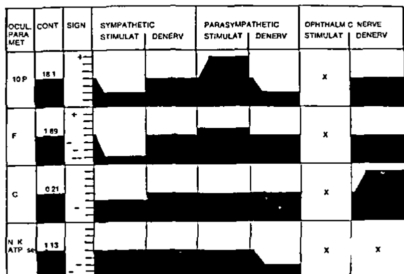


Fig 2

Changes of IOP F C and NaK ATPase during stimulation or 5 days after different types of denervation The changes from the normal level are classified from — — — (decrease) to + + + (increase) thus —/+ corresponds to P < 0 05 — —/+ + to P < 0 01 and — — —/+ + + to P < 0 001

Discussion and conclusions

Our observations indicate that there are special relations between the intraocular dynamics and the nerves running to and from the eye Although we used a relatively large number of animals for this research and applied careful statistical analysis many pitfalls exist (e g) it has to be assumed that Pv stayed constant during the experiments

At present we think that both the sympathetic and parasympathetic mechanisms control the rate of inflow Possibly they regulate different types of systems Possibly in some way the parasympathetic nerve system regulates the »pump» enzyme or NaK-ATP-ase activity in the ciliary body When the nerves are denervated NaK-ATPase activity decreases and IOP is lowered

The results of these studies on the ophthalmic nerve are still preliminary Nevertheless when this nerve was coagulated we found a highly significant increase in the facility of outflow This statistical significance was clear when the operated eyes (7 eyes) were compared not with the contralateral but with the eyes of intact rabbits (27 eyes) This finding might indicate that either the facility of outflow is under the direct control of the trigeminal (ophthalmic) nerve or that the trigeminal (ophthalmic) nerve transmits information centrally and evokes either an inhibition or a stimulation of another nerve centre In turn this sends impulses via its nerve fibres to the eye to regulate the facility of outflow

Further experiments with different types of stimulation in conjunction with denervation and various drugs are in progress

Acknowledgement

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We are also most grateful to Star Ltd Pharmaceutical Manufacturers for supplying us with the laboratory animals

References

Sears M L & Barany E H (1960) Outflow resistance and adrenergic mechanisms *Arch ophthal 64* 839—848

Uusitalo R (1972) Studies on the mechanism regulating the intraocular pressure in the rabbit (Thesis) Acta Instituti Anatomici Universitas Helsinkiensis Suppl 3

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
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Department of Anatomy (Head Professor O Eranko)
University of Helsinki Finland

ELECTRON MICROSCOPICAL STUDIES OF THE ACETYLCHOLINESTERASE POSITIVE AND -NEGATIVE NERVE FIBRES IN THE CILIARY BODY OF THE ALBINO RAT

BY

LEENA RECHARDT ARTO PALKAMA and RISTO UUSITALO

The ciliary processes are innervated in three main ways 1) a sympathetic supply which runs from the upper cervical ganglion partially via the ciliary ganglion along the internal carotid artery to the eye 2) parasympathetic nerves which originate from Edinger—Westphal nucleus synapsing in the ciliary ganglion 3) and somatic sensory nerves which send their branches to the Gasserian ganglion where the cell bodies lie Nevertheless there is some discrepancy about the ganglion cells seen in the ciliary body they are found in some species *e g* in the ciliary body of the human eye (Bryson et al 1966) but not in others

In general the innervation pattern is complex because of the numerous interconnections (Palkama et al 1973) Moreover it varies from species to species The results of recent pharmacological studies have increased the confusion about the functions of either cholinergic or adrenergic mechanisms The present study was carried out by combining histochemical techniques and electron microscopical studies to elucidate the nature of the innervation of the ciliary processes in the eye of the albino rat

Material and methods

The ciliary bodies were fixed either with 2 5 % glutaraldehyde solution or with 2 % potassium permanganate in ice cold Krebs Ringer glucose solution For demonstrating acetylcholinesterases Karnovsky Roots direct coloring thiocholine technique was used with acetylthiocholine as substrate and 10^{-6} M iso OMPA as an inhibitor for non specific cholinesterases (Karnovsky and Roots 1964) The

advantage of this method is that using the electron microscope it is possible to demonstrate the amine-containing dense cored vesicles in the nerve terminals and acetylcholinesterase activity simultaneously

Some rats were pretreated with the monoamine oxidase inhibitor Nialamide as well as L Dopa or noradrenaline Six rats were sympathectomized unilaterally one week before the histochemical studies Parasympathetic stimulation was performed unilaterally on two rats by stereotactic stimulation of the oculomotor nerve (Uusitalo 1972) the eyes being removed immediately and processed for acetylcholinesterase reaction

All the specimens were viewed and photographed without post staining

Results

In light microscopical specimens both the fluorescence-positive and acetylcholinesterase-positive nerve-fibre networks seemed to be roughly identical This correlation was confirmed at the ultrastructural level with both the potassium permanganate and the cholinesterase techniques

In the specimens treated with potassium permanganate both the nerve terminals containg small dense-cored vesicles and terminals with only empty looking vesicles ran in the same nerve bundles possibly surrounded by the same Schwann-cell envelope (Fig 1) These bundles were abundant in the stroma but were also found in the processes close to the epithelial cells and the external limiting membrane Special attention was paid to identifying amine granule containing terminals, which would synapse on the epithelial cells but none could be found After unilateral sympathectomy the small dense-cored vesicles disappeared from the nerves on

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Fig 1

Electron microscopical appearance of the nerve terminals in the ciliary processes of the albino rat One nerve terminal contains only clear synaptic vesicles and the neighbouring one dense cored vesicles (indicated by arrows) Potassium per manganate fixation No post staining (× 74 000)

Fig 2

Specific acetylcholinesterase reaction in the nerve fibres of the ciliary processes of the albino rat The reaction product is concentrated around a large nerve terminal containing clear synaptic vesicle No post staining (× 34 400)

Fig 3

Specific acetylcholinesterase reaction in the nerve fibres of the ciliary processes of the albino rat The enzymatic reaction product is manifested as a discontinuous line around a nerve terminal containing dense cored vesicles (indicated by arrows) No poststaining (× 68 800)

the sympathectomized side Treatment with Nialamide and L-Dopa or noradrenaline increased the number of dense cored vesicles in the terminals

Acetylcholinesterase reaction

Specific cholinesterase reaction was localized around large unmyelinated nerve fibres and terminals which contained clear synaptic vesicles 400 Å in size (Fig 2) In some terminals acetylcholinesterase reaction occurred around the nerve terminals which contained small dense-cored vesicles (Fig 3) After Nialamide and L-Dopa or noradrenaline pretreat-



ments the cholinesterase reaction was still demonstrable around the terminals which now contained more dense-cored vesicles than the con trols After sympathectomy the overall acetylcholinesterase activity had decreased and many nerve fibres and terminals appeared to have degenerated No terminals with both dense-cored vesicles and an acetylcholinesterase reaction could be found

Small unmyelinated nerve terminals with a positive enzyme reaction were seen very seldom close to the epithelial cell these fibres were unchanged after sympathectomy On one occasion an ending with clear synaptic vesicles without an acetylcholinesterase reaction was observed in close apposition to an epithelial cell

After parasympathetic stimulation we could not find increased amounts of the enzymatic reaction product around the nerve terminals a study of other possible ultrastructural chances is in progress

Discussion

Acetylcholinesterase activity which is considered to be one criterion of nervous transmission involving acetylcholine was localized in the same nerve terminals that contained amine granules The finding that these fibres disappeared after sympathectomy strongly favours their origin from the upper cervical ganglion as reported also in the rat pineal body (Eranko et al 1970) This also supports the suggestion of Burn and Rand (1959) that a cholinergic link is concerned in adrenergic transmission Nevertheless the possibility of an axo-axonal interaction among neighbouring nerve fibres cannot be excluded The position of the nerves is similar to that found in the iris (Ehinger et al 1970 and Ivens et al 1973) Applying a cholinesterase technique to a study of the nerves of the iris of the rat Ivens et al (1973) have recently reported very similar findings to our own

No synaptic contacts with true synaptic thickenings on the epithelial cells could be identified, despite the reports of the fluorescing fibres interdigitating between the epithelial cells (Uusitalo and Palkama 1971) Cholinesterase positive thin fibres were located near the epithelial cells whose origin is uncertain Denervation and stimulation studies combined with pharmacological experiments would further elucidate the nature of these fibres

The present study shows beyond question that cholinergic and adre nergic interaction is concerned in the innervation of the ciliary processes

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References

Burn J H & Rand M (1959) Sympathetic postganglion mechanism *Nature (Lond)* *184* 163—165

Bryson J M Wolter J R & O Keefe N T (1966) Ganglion cells in the human ciliary body *Arch Ophthal* *75* 57

Ehinger B Falck B & Sporrong B (1970) Possible axo axonal synapses between peripheral adrenergic and cholinergic nerve terminals Z *Zellforsch* *107* 508—521

Eranko O Rechardt L Eranko L & Cunningham, A (1970) Light and electron microscopic histochemical observations on cholinesterase containing sympathetic nerve fibre in the pineal body of the rat Histochem *J* *2* 479—489

Ivens C Mottran D R Lever J D Presley R & Howells G (1973) Studies on the acetylcholinesterase (Ache) positive and negative autonomic axons supplying smooth muscle in the normal and 6 hydroxydopamine (6 OHDA) treated rat iris Z *Zellforsch* *138* 211—222

Karnovsky M J & Roots L (1964) A direct coloring thiocholine method for cholinesterases *J Histochem Cytochem* *12* 219—221

Palkama A Uusitalo R & Stjernschantz J (1974) Some aspects of nervous control of aqueous humour dynamics in the rabbit eye *Acta ophthal (Kbh)* Suppl *123*

Uusitalo R & Palkama A (1971) Evidence for the nervous control of secretion in the ciliary processes Histochemistry of nervous transmission In Eränko O ed *Progr in Brain Res* *34* Elsevier

Uusitalo R (1972) Effect of sympathetic and parasympathetic stimulation on the secretion and outflow of aqueous humour in the rabbit eye *Acta physiol scand* *86* 315—326

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MORPHOLOGICAL BASIS OF DIFFUSION THROUGH THE IRIS VESSELS IN THE DYNAMICS OF THE AQUEOUS HUMOUR

BY

MATTI SAARI

The ultrastructure of the microcirculatory bed of the iris was examined in an appraisal of the functional significance of the iris vessels in the dynamics of the aqueous humour Aqueous humour was found to have free access to the tubular tissue spaces surrounding the iris vessels Nonfenestrated endothelial cells with micropinocytosis vesicles appeared in the whole microcirculatory bed The vascular wall was thinnest in the capillaries and postcapillary venules where occasionally it was formed by only basement membrane and flattened endothelial cells A relatively wide intercellular space and macula occludens were seen between these cells It is concluded that this intercellular space may account for the »small pore system 4 nm in diameter which enables the diffusion through the iris vessels to occur Larger molecules can pass slowly through the vesicular transport system of the micropinocytosis vesicles

Key words aqueous dynamics — blood aqueous barrier — blood vessels — diffusion — electron microscopy — histology — iris — microcirculation

The aqueous humour is produced by the pars plicata of the ciliary body It flows from the posterior chamber through the pupil into the anterior chamber and leaves the eye mainly through the trabecular meshwork Aqueous humour is separated from the plasma by various barriers with different physiological properties in the anterior and the posterior chambers

In the anterior chamber small molecular substances are exchanged between the blood stream of the iris vessels and the aqueous humour Apart from ascorbate and ureaions about half the total of all other ions enter the aqueous in the anterior chamber by diffusion through the iris vessels and about half by flow from the posterior chamber (Kinsey & Palm 1955)

Gregersen (1959 b) found that dextran molecules about 5 nm in diameter passed from the anterior chamber into the tubular tissue spaces of the iris vessels Thus the wall of the iris vessels seems to be the site of the »blood iris-aqueous barrier»

Not all the walls of the microvessels of the iris have the same structure An electron microscopic study of the pig iris (Saari 1972) showed that the microcirculatory bed could be classified into different components The major arterial circle was an arteriole 50—100 μm in diameter the radial iris arteries being terminal arterioles 15—50 μm in diameter The diameter of the precapillary arterioles was 7—15 μm that of the capillaries less than 8 μm postcapillary venules 8—30 μm and the radial iris veins 30—90 μm

The major arterial circle showed two layers of circular smooth muscle cells the radial iris arteries one layer and the precapillary arterioles an incomplete layer (Saari 1972) A thick basal lamina with a fragmentary elastica interna was seen in the major arterial circle The basal lamina was thinnest in the capillaries and in the postcapillary venules The narrow and thick endothelial cells in the major arterial circle gradually widened and thinned towards the capillaries so that in many places the walls of the capillaries and postcapillary venules consisted only of thin endothelial cells and basement membrane (Saari 1972) Thus the vascular wall was structurally weakest in the capillaries and postcapillary venules

Lipid soluble substances such as oxygen and carbon dioxide pass rapidly through the endothelial cells For lipid insoluble molecules the endothelial cells of the iris vessels form a semipermeable barrier This barrier may be composed of two systems — »a small pore system» (Karnovsky 1967 Hammersen 1971) and a »vesicular transport system In the iris vessels the former may be assumed to be permeable to water and lipidinsoluble substances up to 4 nm in diameter The diffusion through the iris vessels occurs through this pathway The slow passage of molecu les larger than the small pores occurs via the vesicular transport system

Non fenestrated endothelium has been seen in the whole area of the microcirculatory bed of the pig iris (Saari 1972) and hence endothelial cell fenestrations are not responsible for diffusion through the iris vessels

Contiguous endothelial cells were found to have a tight junction in the major arterial circle The intercellular junction became gradually weaker towards the capillaries A relatively wide intercellular space and macula occludens were seen at the intercellular junctions of the endothelial cells in capillaries and postcapillary venules (Saari 1972) The vascular permeability gradient (Rous Gilding & Smith 1930) can be explained on this morphological basis while the variable intercellular spaces in the capillaries and postcapillary venules may form the small pore system, through which small molecules pass from the vessel lumen into the aqueous humour and vice versa Thus the diffusion through the iris vessels in the aqueous humour dynamics is made possible

Micropinocytosis vesicles of about 66 nm have been seen in the endothelial cells of the iris vessels (Saari 1972) and probably have a fundamental role in the active transport of fluid and solutes across the endothelial cell (Fawcett 1966 Hammersen 1971) The existence of this vesicular transport system explains how the slow transcapillary exchange of high molecular substances occurs Possibly plasma proteins hormones and antibodies pass across the endothelium by this means (Karnovsky 1967)

Pinocytosis vacuoles 340—650 nm in diameter have also been seen in the iris vascular endothelial cells (Saari 1972) They are formed by the marginal folds as described by Fawcett (1966) These vacuoles move too slowly to explain the diffusion through the iris vessels in physiological states

The basement membrane was found to be continuous with no fenestrations apart from pericyte-endothelial cell and myoendothelial junctions which were lined by outer basement membrane of the pericyte or muscle cell (Saari 1972) Thus normally the basement membrane cannot be assumed to leak because of fenestration but to function like an ultrafilter Horseradish peroxidase passes freely through the basement membrane (Karnovsky 1967) but conversely large particles such as colloidal carbon are retained by the basement membrane after abnormal vascular leakage (Ashton & Cunha-Vaz 1965)

The iris vessels allowed the passage of trypan blue (Cunha-Vaz Shakib & Ashton 1966) They were impermeable to horseradish peroxidase (Shiose 1971 Smith 1971) a protein 4 4—4 7 nm in diameter Much further work with tracer techniques is required however to establish the structural basis of the normal process of diffusion through the iris vessels

After paracentesis dextran particles of 5—8 5 nm diameter could pass from the anterior chamber into the iris vessels (Gregersen 1959 a)

Paracentesis and local injection of histamine increased vascular permeability by separating the endothelial cells at their margins (Ashton & Cunha Vaz 1965) Peroxidase leakage into the aqueous humour induced by paracentesis occurred earlier through the iris vessels than through the ciliary epithelium (Shiose 1971) Similarly changes in the permeability of the iris vessels may underlay some of the changes in aqueous humour dynamics in some diseases of the anterior eye and in some forms of glaucoma

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References

Ashton N & Cunha-Vaz J G (1965) Effect of histamine on the permeability of the ocular vessels *Arch Ophthal 73* 211—223

Cunha Vaz J G Shakib M & Ashton N (1966) Studies on the permeability of the blood retinal barrier I On the existence development and site of a blood retinal barrier *Brit J Ophthal 50* 441—453

Fawcett D W (1966) *The cell its organelles and inclusions An atlas of fine structure* Saunders Philadelphia

Gregersen E (1959 a) Elimination of high- and low molecular dextran fractions from the anterior chamber and iridic stroma of rabbit eyes *Acta ophthal* (Kbh) *37* 35—48

Gregersen E (1959 b) The tubular tissue spaces surrounding the endothelial channels of the human iridic vessels Histology and postfoetal development of the tissue spaces *Acta ophthal* (Kbh) *37* 199—208

Hammersen F (1971) *Anatomie der terminalen Strombahn* Muster Feinbau Funktion Urban & Schwarzenberg Munchen

Karnovsky M J (1967) The ultrastructural basis of capillary permeability studied with peroxidase as a tracer *J Cell Biol 35* 213—236

Kinsey V E & Palm E (1955) Posterior and anterior chamber aqueous humor formation *Arch Ophthal 53* 330—344

Rous P Gilding H P & Smith F (1930) The gradient of vascular permeability *J exp Med 51* 807—830

Saari M (1972) Fine structure of the microcirculatory bed of the pig iris *Ann Med exp Fenn 50* 12—23

Shiose Y (1971) Morphological study on permeability of the blood aqueous barrier *Jap J Ophthal 15* 17—26

Smith R S (1971) Ultrastructural studies of the blood aqueous barrier I Transport of an electron dense tracer in the iris and ciliary body of the mouse *Amer J Ophthal* 71 1066—1077

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AXONAL TRANSPORT IN THE RETINAL GANGLION CELLS OF THE RABBIT UNDER DIFFERENT EXPERIMENTAL CONDITIONS

BY

J SJÖSTRAND and J O KARLSSON

The axonal transport of protein in the retinal ganglion cells of the rabbit was studied after the intraocular injection of ^{3}H leucine Colchicine had profound effects on this transport system

Axonal transport both the migration rate and the amount was found to be virtually normal in rabbits totally deprived of light from birth Retrograde transneuronal changes were examined in the retinal ganglion cells one month after unilateral lesions of the visual cortex The incorporation of tritiated leucine into the retina connected with the operated visual cortex was decreased The amounts of slowly migrating protein destined for the lateral geniculate and superior colliculus were appreciably reduced on both the operated and unoperated side whereas the relative amounts of protein transported by rapid axonal transport showed no change

After intraocular injection of ($^{1-5}$I) labelled albumin no clear evidence for a antero- or a retro grade transport of macromolecules originating or terminating in the eye could be obtained

Key words axonal transport — protein synthesis — retinal ganglion cells

Neurons are characterized by their uniquely long processes Axonal constituents are known to be transported from the cell body down the axon to the nerve terminals (for review see Lasek 1970) The axon and axon

terminal depend on intracellular transport of proteins from the perikaryon since no efficient intraneuronal system for protein synthesis has been shown to exist outside the nerve cell body Nevertheless little is known about the regulation of axonal transport during conditions which produce morphological and biochemical changes in the nerve cell body or its processes

Here we review some of our recent studies on axonal transport in the optic system of the rabbit during different conditions Previous studies on axonal transport in retinal ganglion cells have shown the presence of at least four different transport phases (Karlsson & Sjostrand 1971 a) The present study aimed to determine the effect of colchicine treatment light deprivation and cortical lesions on axonal transport

Material and methods

Albino rabbits of both sexes weighing between 2 and 3 5 kg were used In all experiments carried out to study retinal protein synthesis and axonal transport of isotopically labelled proteins 50 μCi of L (4 5 ^{3}H) leucine (The Radiochemical Centre Amersham England) was injected into the vitreous body of one or both eyes (Karlsson & Sjostrand 1971 a) All operations or injections were performed under pentobarbital anesthesia

At various intervals after the isotope injection the rabbits were killed by an overdose of sodium pentobarbital given intravenously The various parts of the optic pathway were dissected out (Karlsson & Sjostrand 1971 a) and homogenized in 5 % TCA containing 10 mM leucine After centrifugation the samples were washed with additional TCA and subsequently extracted with chloroform methanol (2 1 v/v) The protein precipitate was dissolved in soluene^{R} (Packard Co) and its radioactivity determined by liquid scintillation counting (Karlsson & Sjostrand 1971 a) Similarly radioactivity in the TCA soluble material was also measured

Colchicine Colchicine (1—100 μg) dissolved is 50 μl distilled water was injected intraocularly at various intervals before isotope injection or electro physiological recording

Light deprivation Pregnant rabbits were placed in separate cages where the litters were born and housed in a completely dark room throughout the experiment Two and a half months after birth when they weighed 1 8—2 2 kg the rabbits were transferred individually to a separate room and injected with ^{3}H leucine into both eyes During the injections the animals were exposed to a very weak red light from a Kodak Wratten filter (Type 1 M) for about 10 min After the injections the animals were returned to the dark room

Removal of the visual cortex The animals were anaesthetized and an occipital craniotomy was performed Visual areas I and II in the left occipital lobe were removed by suction No gross neurological deficit and no signs of infection were noted after these operations As a check on surgical trauma a group of animals were subjected to a sham operation In these rabbits the occipital craniotomy

was followed by an incision in the dura and a minimal brain lesion was made in the left occipital cortex After an interval of one month the rabbits were given injections of ^3H leucine into both eyes

Intraocular injections of exogenous protein Rabbits were injected with 50 μl of a solution of (^{125}I) labelled human serum albumin (^{125}I HSA sp act 0 155 mCi/mg conc 1 mCi/ml AB Atomenergi Studsvik Sweden) into the vitreous body of the left eye In some animals the (^{125}I) HSA solution was injected together with concanavalin polylysine or polyornithine At specified intervals after the injections the animals were killed and the radioactivity of the various parts of the optic system determined as already described

Results and discussion

Colchicine

The mechanism responsible for the transport of proteins in the axon is not yet known for certain though the microtubules have been implicated in this (Kreutzberg 1969 Dahlstrom 1968 Karlsson & Sjostrand 1969 Karlsson *et al* 1971) because colchicine (which causes a change in microtubules) can block axonal transport

After an intraocular injection of colchicine protein synthesis in the retina is not depressed (Karlsson *et al* 1971) If 2 5 μg or more colchicine is injected into the eye 24 h before the isotope is injected the rapid phase of axonal transport is almost completely inhibited 2 5 μg of colchicine produces about 90 per cent inhibition and 10 μg about 95 per cent inhibition of the rapid transport phase Colchicine seems to have a relatively long lasting effect even after intervals between 8 and 47 days the rapid phase is still found to be inhibited

In contrast to the rapid phase of axonal transport the slow phase seems to be more resistant to colchicine treatment 2 5 μg producing only about 50 per cent and 10—25 μg colchicine about 85 per cent inhibition

To evaluate the influence the nerve cell body exerts on the axon and its terminals we have recently studied the effect of transport inhibition on the synaptic transmission in the superior colliculus (Andersson *et al* in preparation) Using an electrophysiological technique we studied the evoked response in the superior colliculus to optic nerve stimulation in colchicine treated animals 4 days after an intraocular injection of 25 μg colchicine our preliminary results show that the amplitude of the response in the superior colliculus connected with the treated eyes decreased (Andersson *et al* in preparation) Similarily Perisic & Cuenod (1972) found an appreciable depression of tectal responses to electrical stimulation in pigeons 3 days after the intraocular injection of colchicine

The results of these studies suggest that synaptic transmission may depend on a continuous supply of material by axonal flow In denervated synapses in the lateral geniculate nucleus of the cat the ultrastructural and electrophysiological changes with time are related to the length of the distal axon stump of the retinal ganglion cells (Saavedra *et al* 1971) The differences in the temporal course of the denervation after eye enucleation and a lesion of the optic tract may be interpreted as being due to a decrease in the terminals of material migrating with fast axonal flow

Light deprivation

The visual system is a suitable model for studying the effects of sensory deprivation on neuronal systems Rearing an animal in complete darkness from birth produces several morphological and/or biochemical changes in the retina the lateral geniculate body and the visual cortex (for review see Cowan 1970) We aimed to study the axonal transport of protein in retinal ganglion cells of rabbits reared in darkness from birth (Karlsson & Sjostrand 1971 b) We found that no appreciable changes in protein metabolism occur in the retina of light-deprived animals compared with normal animals

After an intraocular injection of (^{3}H)leucine the isotope is rapidly incorporated into the retinal proteins the process being complete within a few hours There was evidence that in the light deprived animals the total protein synthesizing capacity of the retina was depressed the half-life of retinal proteins was about 6 days that is within normal limits Moreover the amount of labelled protein reaching the lateral geniculate body by rapid axonal transport was much the same in light deprived and in normal animals No appreciable differences were noticed either in the proportion of rapidly transported labelled proteins or in the rate of transport in the optic nerve and tract Finally there were no differences in the relative levels of rapid and slow axonal transport in the two groups of rabbits indicating that these phases are relatively independent of light stimulation of the retinal ganglion cells

Since in dark-reared animals the axons of the optic nerve also show impulse propagation (Burke & Hayhaw 1968) our study provides no direct information about the relation between axonal flow and electrical activity In a study of mice with hereditary degeneration of the visual receptors Grafstein *et al* 1972 showed that the rate of slow axonal trans port in the retinal ganglion cells was decreased This study suggests that a link exists between axonal transport and electrical activity

Transneuronal effects after removal of the visual cortex

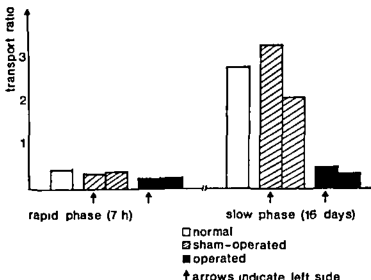
In agreement with the findings of Chow & Dewson (1966) we found that severe retrograde degeneration occured in the lateral geniculate body after removal of the ipsilateral visual cortex One month after inducing the lesion in the left visual cortex histological examination showed that about 70 to 90 per cent of the neurons of the ipsilateral lateral geniculate body had disappeared The lateral geniculate body on the intact side and the superior colliculus on both sides remained normal and no cell degeneration could be observed This type of lesion interrupts axons from geniculate-cortical neurons leading to a retrograde cell degeneration of the affected cell bodies In addition cortico geniculate cortico-collicular and other neurons degenerate Thus the retinal ganglion cells loose their primary target cells in the lateral geniculate body The retinal projection to the superior colliculus does not loose any primary target cells since there is no direct collicular cortical projection

Our investigation (Karlsson *et al* in preparation) was focused on changes in protein synthesis and axonal transport of proteins in retinal ganglion cells induced by this unilateral ablation of the visual cortex

There was slightly decreased incorporation of (^{3}H)leucine in the retina connected to the operated visual cortex compared with the other retina This slight diminution in retinal protein synthesis is probably due to retrograde transneuronal effects caused by the loss of primary target cells Morphological changes in the retina after cortical ablation has already been noted (Ganser 1882 Monakow 1889 Van Buren 1963) particularly when the brain lesion was induced in very young animals (see Cowan & Wenger 1968)

To relate the amount of protein transported to the nerve terminals to the amount of protein synthesis in the contralateral retina our data in Fig 1 were expressed as percent of transported radioactivity compared with the total amount of proteinbound radioactivity in the contralateral retina Evidently the lesion in the left visual cortex did not appreciably change the relative amounts of protein aimed for rapid axonal transport either ipsilaterally or contralaterally On the other hand the lesion did appreciably affect slow axonal transport to both the lateral geniculate body and the superior colliculus this was roughly 2 to 5 times less in the operated animals

This contralateral effect of the lesion on slow axonal transport may be mediated by several mechanisms firstly effects on specific transcallosal fibers from the operated visual cortex secondly some mechanism



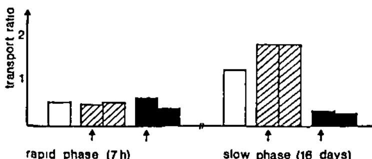


Fig 1

Data in this figure are expressed as transported radioactivity in percent of radioactivity incorporated into retinal proteins of the contralateral eye 7 h after injection i e *at a time when maximal amount of (^3H) leucine is incorporated into* retinal protein (Karlsson and Sjostrand 1971 a) Average values from normal animals calculated from Karlsson and Sjostrand (1971 a 1972) Values from sham operated animals are the average of results in two rabbits The transport ratio for the superior colliculus on operated animals compared with that of normal animals was similar at 16 days and at 27 days after injection

Table 1

Radioactivity expressed as disintegrations per min in different regions after an intraocular injection of 50 μCi [1] I HSA into the left vitreous body

Time after injection (hours)	Lateral geniculate body left	Lateral geniculate body right	Superior colliculus left	Superior colliculus right	Ciliary body left	Ciliary body right	Superior cervical ganglion left	Superior cervical ganglion right
2	4 500	1 450	2 500	3 000	—	—	11 800	15 900
2	2 000	1 400	1 900	1 940	—	—	6 000	4 400
7	1 650	3 460	2 500	3 380	—	—	8 600	3 [illegible]0
7	730	1 000	1 010	1 200	2 910	2 300	11 600	2 380
17	790	770	1 240	1 360	3 600	2 100	1 200	1 650
24	890	1 130	610	1 200	2 100	4 300	1 750	3 300
24	1 870	1 000	710	950	—	—	2 340	1 260
31	4 400	5 260	6 900	10 000	7 450	3 060	6 800	2 350
31	5 000	5 000	4 150	5 150	—	—	2 340	1 600
7 days	960	1 760	1 100	910	2 700	1 260	2 650	2 380

operating at the retinal level caused by the very few fibres which remain uncrossed in the optic chiasm (Polyak 1957) or thirdly some systemic factor

Neuronal uptake and axonal transport of exogenous proteins

The phenomenon of retrograde axonal transport of exogenously administered substances can be shown in some experimental systems but not in others (for review see Kristensson & Olsson 1973) To test both anterograde and retrograde axonal transport of an exogenous macromolecule we injected ([1] I) labelled albumin or peroxidase into the eye of adult rabbits (Hansson *et al* in preparation) Anterograde transport was tested in retinal ganglion cells Retrograde transport was tested in two types of neurons both of which have their axon terminals in the iris — the parasympathetic neurons of the ciliary ganglion and the sympathetic neurons originating in the superior cervical ganglion

Retinal uptake The uptake of the intraocularly injected ([1 5]I) HSA in the retina reached a maximal level 7 h after injection when about 3 % (corresponding to 10 μg albumin) of the injected isotope was recovered A similar amount of isotope was found in the iris The retinal uptake

of ($^{1\ 5}$I)-HSA seemed to be lower than that reported for several amino acids (Karlsson & Sjostrand 1972)

Anterograde transport There was no axonal transport of ($^{1\ 5}$I) HSA from the retina to the nerve terminals in the lateral geniculate body or in the superior colliculus (Table I) Small amounts of label were found in the nerve terminal regions on the same and opposite sides as the intraocular injection

Retrograde transport We could find no retrograde axonal transport of (^{125}I) HSA from the parasympathetic and sympathetic nerve terminals in the iris to the corresponding ganglia the ciliary ganglion and the superior cervical ganglion (Table I) Possibly a little label was transported to the superior cervical ganglion at 7 h (Table I)

It was not possible to increase retinal uptake or to detect any antero or retrograde axonal transport of (^{1} I) HSA by adding concanavalin (500 μg) polylysine (10 μg) or polyornitine (10—100 μg) to the injection solution

These experiments did not provide any clear evidence for a antero or retro-grade transport of macromolecules in axons originating or terminating in the eye of the adult rabbit Both biochemical and morphological techniques demonstrated uptake ($^{1\ 5}$I) HSA and peroxidase in retinal ganglion cells and in nerve fibres in the iris Thus factors such as diffusion barriers for the tracer were not responsible for the negative results We could not exclude that a rapid retrograde axonal transport of a little (^{1} I)-HSA had reached the superior cervical ganglion at 7 hours (Table I) Hence axonal transport of exogenous macromolecules may occur in the studied cells but at too low a level to be detected with our experimental technique Such a transport may be important in the axons of immature animals (LaVail & LaVail 1972 Kristensson & Olsson 1973)

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References

Van Buren J M. (1963) Trans synaptic retrograde degeneration in the visual system of primates *J Neurol Neurosurg Psychiat 26* 402

Burke W & Hayhow W R (1968) Disuse in the lateral geniculate nucleus of the cat *J Physiol (Lond) 194* 495—519

Chow K L. & Dewson J H (1966) Numerical estimates of neurons and glia in lateral geniculate body during retrograde degeneration *J Comp Neur 128* 63—74

Cowan W M & Wenger E (1968) Degeneration in the nucleus of origin of the preganglionic fibers to the chick ciliary ganglion following early removal of the optic vesicle *J Exp Zool 168* 105—124

Cowan W M (1970) Anterograde and retrograde transneuronal degeneration in the central and peripheral nervous system. In Contemporary research methods in neuroanatomy p 217—251 Springer-Verlag Berlin Heidelberg New York

Dahlstrom A (1968) Effect of colchicine on transport of amine storage granules in sympathetic nerves of rat *Europ J Pharmacol 5* 111—113

Ganser S (1882) Ueber die periphere und centrale Anordnung der Sehnervenfasern und uber das Corpus bigeminum anterius Psychiatrie und Nerven krankheiten p 341—381 Verlag von August Hirschwald

Graf tein B Murray M & Ingoglia N A. (1972) Protein synthesis and axonal transport in retinal ganglion cells of mice lacking visual receptors *Brain Res 44* 37—48

Karlsson J O & Sjostrand J (1969) The effect of colchicine on the axonal transport of protein in the optic nerve and tract of the rabbit *Brain Res 13* 617—619

Karlsson J O & Sjostrand J (1971) Synthesis migration and turnover of protein in retinal ganglion cells *J Neurochem 18* 749—767

Karlsson J O & Sjostrand J (1971) Effect of deprivation of light on axonal transport in retinal ganglion cells of the rabbit *Brain Res 29* 315—321

Karlsson L O Hansson H-A & Sjostrand J (1971) Effect of colchicine on axo nal transport and morphology of retinal ganglion cells *Z Zellforsch 115* 265—283

*Karlsson J O & Sjostrand J (1972) Axonal transport of proteins in retinal gan*glion cells Amino acid incorporation into rapidly transported proteins and distribution of radioactivity to the lateral geniculate body and the superior colliculus *Brain Res 37* 279—285

Kreutzberg G W (1969) Neuronal dynamics and axonal flow IV Blockage of intra axonal enzyme transport by colchicine *Proc nat Acad Sci (Wash) 62* 722—728

Kristensson K. & Olsson Y (1973) Diffusion pathways and retrograde axonal transport of protein tracers in peripheral nerves *Progress in Neurobiology* Vol 1 Part 2

Lasek R J (1970) Protein transport in neurons *Int Rev Neurobiol 13* 289

La Vail J H & La Vail M M (1972) Retrograde axonal transport in the central nervous system. *Science 176* 1416

Monakow von C (1882) Experimentelle und pathologisch anatomische Untersuchungen uber die optischen Centren und Bahnen *Arch Psychiat Nervenkr* 20 714—789

Perisić M & Cuenod M (1972) Synaptic transmission depressed by colchicine blockade of axoplasmic flow *Science* 175 1140—1142

Polyak S (1957) The vertebrate visual system (Ed Kluver H) The University of Chicago Press Chicago

Saavedra J P Vaccarezza O L Reader T A & Pasqualini E (1971) Ultrastructural and electrophysiological aspects of denervated synapses in the lateral geniculate nucleus Vision Res Suppl 3 229—238

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Discussion

J Sjostrand In a recent study (Karlsson & Sjostrand 1972) we have studied the uptake of several different amino acids after intraocular injection Interestingly enough the relative proportion of the newly synthesized retinal proteins aimed for axonal transport is rather similar for the different amino acids even though the total retinal incorporation differs

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Department of Anatomy (Head Professor O Eranko)
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EFFECT OF SHORT-TERM INCREASED INTRAOCULAR PRESSURE ON THE FINE STRUCTURE OF THE RETINA

BY

PEKKA RUUSUVAARA and ARTO PALKAMA

Much is already known about the histological changes in the optic nerve and retina in the eyes of patients with raised intraocular pressure Moreover numerous experimental investigations mainly with the light microscope have been made in different animal species on the effect of glaucoma on the optic nerve and retina (see e g Flocks *et al* 1959 Zimmerman *et al* 1967 Lessell & Kuwabara 1969) These reports have mainly described changes in the optic nerve head and retina in eyes with long-term hypertension On light microscopy oedema of the nerve fibre layer and ganglion cell layer can be observed in rabbit retina 24 hr after inducing ocular hypertension (de Carvalho 1961) Kalvin *et al* (1965) observed appreciable retinal changes produced by α-chymotrypsin induced glaucoma the retina was severely damaged with the photoreceptors absent or considerably altered and fewer ganglion cells than usual In owl monkeys made glaucomatous with α-chymotrypsin Lessel *et al* (1969) found retinal atrophy in the pigment epithelium though the *ganglion cells were intact*

The present investigation aimed to find out the early fine-structural changes in the rabbit retina in conditions corresponding to those in acute glaucoma Ocular tension was increased rapidly to about 50 to 80 mm

Hg by infusing saline into the anterior chamber The pressure was maintained at the same level for 2—5 hr and measured throughout the experiment in both eyes In the same experiment we tried to find out the effect of short-term ocular hypertension on the fine structural localization of acetylcholinesterase activity

Material and methods

Three albino and three pigmented male rabbits were used in the experiment They were anesthetized by i v injection of 25 % urethane 1 0—1 75 g/kg and the right eye subjected to increased intraocular pressure by infusing saline through a needle into the anterior chamber At the same time the intraocular pressure was measured through the same needle by using a pressure transducer and recorder (Harkonen *et al* 1972) The left eye was used as a control and its intraocular pressure was also measured at the same time In four animals the intraocular pressure was increased in *the experimental eyes to 50—55 mmHg and* in two *to 80* mmHg In the former group the increase was maintained for 5 hr and in the latter for 2 hr After killing the animals the eyes were fixed in 2 5 % glutaraldehyde (phosphate buffer pH 7 2) for 4 hr Those specimens used for morphological studies were further post fixed in 1 % osmium tetroxide for 1 hr thereafter dehydrated and embedded into epon araldite

Some of the glutaraldehyde-fixed specimens were subjected to histochemical studies After fixation these specimens were washed in buffer solution (0°C) overnight Thereafter the specimens were incubated for acetylcholinesterase activity (AChE) according to a modified Koelle technique (Lewis & Shute 1966) The specimens were dehydrated and embedded in epon araldite

Finally the specimens were dissected with LKB ultratome and viewed with the electron microscope (Philips 300)

Results

Macroscopically comparing both groups of eyes no clear-cut differences were observed except for cloudiness and final rupture of the corneas in the high-pressure group (for this reason the pressure could not be maintained at 80 mmHg for longer than 2 hours)

In the *pigment cell layer* of the pigmented rabbits the granules seemed normal Many of these cells contained large intracellular vacuoles with no membranes and being surrounded by the pigment granules No clear-cut changes were seen in other cell organelles (*e g* mitochondria)

In the *rods* large intracellular cysts were seen between the lamellae at the junctional area between the inner and outer segments (Fig 4) No such vesicles were seen in the control specimens Apart from these

vesicles the lamellae of the rods seemed to be intact (Fig 4) The connecting stalk showed a normal structure (Fig 4) as did the axon connections and terminals in the area of the *external plexiform layer* The synaptic ribbons looked normal and were surrounded by intact vesicles

In the *bipolar cell layer* the mitochondria of the bipolar cells on the experimental side were enlarged and their cristae had almost totally disappeared The cell membrane as well as the nucleus and other intracellular organelles were apparently intact Similar changes were seen in the amakrin cells and in the horizontal cells

On the experimental side the area of *internal plexiform layer* axons contained numerous large vesicles probably mitochondrial in origin (Fig 2) These enlarged vesicles contained a triple membrane and occasionally shadows of destroyed cristae (Fig 2) Conversely the synaptic connections and vesicles had apparently remained unchanged (compare Figs 1 and 2) Under higher magnification the axon terminals were seen to be filled with the enlarged mitochondria

Those *ganglion cells* subjected to the increased intraocular pressure also showed enlarged mitochondria (Fig 3 and 5) The mitochondrial cristae were almost totally destroyed Other cytoplasmic organelles *e g* Golgi apparatus also seemed to be enlarged (Fig 3)

The *acetylcholinesterase activity* was localized in both the control and experimental retinas in the ganglion cells amakrin cells internal plexiform layer and nerve fibre layer In the amakrin cells and in the ganglion cells the activity was localized in the ergastoplasmic reticulum nuclear membranes and cell membranes (Fig 5) In the internal plexiform layer and in the nerve fibre layer the enzyme activity was localized at the axonal membranes (Fig 5)

Discussion

The results obtained in the control eyes correspond well with earlier findings (Prince 1964) Hence the anesthesia we used did not cause the changes seen in the experimental eyes Morphological changes were seen in almost all layers of the retina As a general change we found that the mitochondria were very susceptible to the high pressure although in the rod inner segments and pigment epithelium they were more resistant than elsewere in the retina The Golgi apparatus and the endoplasmic reticulum often seemed to be swollen In the pigment epithelium and outer segment of the rods large cysts were seen

Hypertension did not affect the localisation of acetylcholinesterase activity

Previous reports have stated that the ganglion cells and the nerve fibres are the most sensitive structures in the retina to increased intraocular pressure Nevertheless our findings indicate that rods and bipolar cell layer and their connections also show pathological changes even during short-term hypertension To what extent these changes are irreversible and why remain open to question whether the deprivation of retinal and possibly also choroidal blood flow or a direct effect of increased pressure on the retinal cells is difficult to answer on the basis of our present electron microscopic findings

The results obtained indicate that the retinal damage caused by increased intraocular pressure occurs right at the beginning of hypertension in all retinal layers At the beginning it seems to affect mainly those cell elements which are vital for cellular metabolism *e g* mitochondria Conversely structures and enzyme activities associated with nervous transmission are possibly destroyed at a later stage of the hypertension

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Fig 1

High power magnification of the inner plexiform layer of a normal eye Mito chondrial cristae (M) and a synapse (S) with synaptic vesicles are seen (× 68 000)

Fig 2

Axon terminal in the inner plexiform layer of an experimental eye Note the swollen mitochondria (M) with broken inner structures The synapse (S) with synaptic vesicles is morphologically normal (× 138 000)

Fig 3

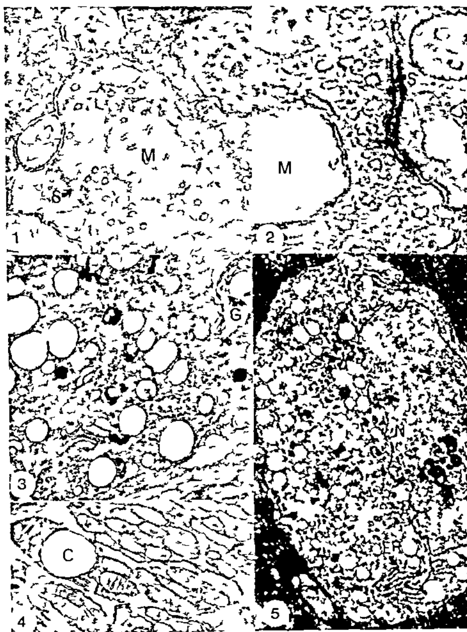
Ganglion cell cytoplasm in a hypertensive eye with large amounts of swollen mitochondria and distended Golgi apparatus saccules (G) (× 18 000)

Fig 4

Microphotograph from the outer and inner segments of the visual cell layer In the membranous part of a rod cyst formation is seen between the lamellae (C) The mitochondria appear normal (× 15 000)

Fig 5

Acetylcholinesterase activity in a ganglion cell from an experimental eye Note the normal activity in the ergastoplasmic reticulum (ER) and nuclear membrane (N) Large swollen mitochondrias are seen (× 10 000)


M
6
1
M
S
2
G
3
N
C
4
ER
5

References

deCarvalho C A (1962) Histopathology of retina and optic nerve with experimental glaucoma *Arch Ophthal 67* 483

Flocks M Tsukahara I & Miller J (1959) Mechanically induced glaucoma in animals Preliminary perfusion and histologic studies *Amer J Ophthal 48* 11

Harkonen M A Palkama A & Uusitalo R (1972) Functional dependence of the ciliary epithelium ATP ase activity and intraocular pressure on the autonomic nervous system *Acta physiol scand*

Kalvin N H Hamasaki D I & Gass J D M (1966) Experimental glaucoma in monkeys I Relationship between intraocular pressure and cupping of the optic disc and cavernous atrophy of the optic nerve *Arch Ophthal 76* 82

Lessell S & Kuwabara T (1969) Experimental alphachymotrypsin glaucoma *Arch Ophthal 81* 853—64

Lewis P R & Shute C C D (1966) The distribution of cholinesterase in cholinergic neurons demonstrated with the electron microscope *J Cell Sci 1* 381

Prince J (1964) The rabbit in eye research C C Thomas USA

Reale E Luciano L & Spitznas M (1970) The fine structural localization of acetylcholinesterase activity in the retina and optic nerve of rabbits *J Histochem Cytochem 19* 85—96

Zimmerman L E de Venecia G & Hamasaki D I (1967) Pathology of the optic nerve in experimental acute glaucoma *Invest Ophthal 6* 109

Discussion

S-E Nilsson The cell damage that you demonstrated such as swollen or »blown out» mitochondria in cells at different levels of the retina can typically be seen after blocking the circulation An intraocular pressure raised to 80 mmHg (as in your experiment) in a rabbit seems to exceed the arterial blood pressure in the eye and might affect not only the retinal circulation but also to a certain extent the choroidal circulation Therefore, it cannot be excluded that the retinal changes described in your paper were caused by circulatory block rather than by intraocular pressure *per se*

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DOSE RESPONSE ANALYSIS OF 0 1 % 0 5 % 1 0 % AND 2 0 % EPINEPHRINE IN CHRONIC OPEN ANGLE GLAUCOMA

BY

AHTI TARKKANEN and LEILA LAATIKAINEN

The effect of instillation of a single drop of 0 1 % 0 5 % 1 0 % and 2 0 % epinephrine borate in an aqueous vehicle on the intraocular pressure was studied in 23 eyes of 12 patients with open angle glaucoma Seventeen eyes were untreated and in six eyes all treatment was discontinued one week before the study After initial applanation tonometry a single drop of epinephrine was instilled in both eyes at 8 a.m. Applanation measurements were repeated after 2 4 and 8 hours On successive days the effect of 0 1 % 0 5 % 1 0 % and 2 0 % epinephrine was studied in the same group of patients so that the eyes acted as their own controls

The maximal pressure reduction was obtained with 0 5 % or 1 0 % solution. A significant effect was seen two hours after instillation and this continued for at least 8 hours With 0 1 % solution a significant pressure reduction was also observed after eight hours The effect of 2 0 % epinephrine solution was slower somewhat weaker and shorter than the effect of 0 5 % and 1 0 % solutions In clinical practice the use of this epinephrine compound in aqueous vehicle is indicated from 0 1 % to 1 0 % solutions The most appropriate concentration for each patient has to be tested individually using the single drop technique

Key words open angle glaucoma — epinephrine — treatment

show an equal response to stronger solutions on the other hand some poor responders to 0 5 % solution reacted well to 1 0 % epinephrine No particular concentration was found to be generally the best This has to be established individually using the single-drop technique

Discussion

Epinephrine diminishes the intraocular pressure by decreasing aqueous secretion (Weekers et al 1955) and also improving the outflow facility (Ballantine & Garner 1961 Vannas & Linkova 1973)

The slow but significant pressure reducing effect of 0 1 % epinephrine solution in eyes with both normal and subnormal outflow facility may indicate a decreased aqueous secretion due to a low epinephrine concentra tion At higher concentrations the pressure-reducing effect occurred faster and was more definite in eyes with subnormal outflow facility possibly owing to an action on the outflow as well Similar findings have been reported by Eakins (1963) and Lorenzetti (1971) in studies on rabbit eyes Eakins and Lorenzetti have suggested that sympathetic beta-receptors are activated at low doses and alpha-receptors at high doses of epinephrine

When the concentration of epinephrine was increased to 2 0 % the pressure reduction was slowed and did not last so long as with the weaker solutions This may be due to direct vascular effects of epinephrine on the anterior uvea such as reactive vasodilation and increased permeability of the iris and ciliary vessels after the primary vasoconstriction Hence epinephrine borate in this vehicle should be used only up to a concentration of 1 %

Reductions in the concentrations of other antiglaucomatous drugs have also been recommended For instance increase in pilocarpine concentration above 4 % does not increase the response in patients who are improved by this drug (Harris & Galin 1970 Drance & Nash 1971) Simi larly it is possible to decrease the concentration of phospholine iodide from 0 25 % to 0 06 % (Harris 1972) The effects of more viscous vehicles or binding of the drug into slower polypeptide capsules was outside the scope of this study nor did it aim to deal with the effects of the use of epinephrine for several weeks on the various indices of intraocular fluid dynamics

References

Ballantine E J & Garner L. L. (1961) Improvement of the coefficient of outflow in glaucomatous eyes *Arch Ophthal 66* 314—317

Drance S M & Nash P A (1971) The dose response of human intraocular pressure to pilocarpine *Canad J Ophthal 6* 9—13

Eakins K E (1963) The effect of intravitreous injections of norepinephrine epinephrine and isoproterenol on the intraocular pressure and aqueous humor dynamics of rabbit eyes *J Pharmacol exp Ther 140* 79—84

Harris L S (1972) Comparison of pilocarpine and echothiophate iodide in open angle glaucoma *Ann Ophthal 4* 736—743

Harris L. S & Galin M A (1970) Dose response analysis of pilocarpine induced ocular hypotension *Arch Ophthal 84* 605—608

Kitazawa Y (1972) Dose response analysis of ocular hypotensive effects of epinephrine and norepinephrine *Jap J Ophthal 16* 30—38

Langham M E (1969) New developments in the adrenergic pharmacology of normal and glaucomatous eyes *Trans Austr Coll Ophthal 1* 5?—63

Lorenzetti O J (19?1) Dose dependent influence of topically instilled adrenergic agents on intraocular pressure and outflow facility in the rabbit *Exp Eye Res 12* 80—87

Vannas S & Linkova M (1973) Adrenalin therapy in glaucoma XX Meeting of Nordic Ophthalmologists Reykjavik 1971 *Acta ophthal (Kbh)* Suppl 120 39—44

Weekers R Delmarcelle Y & Gustin J (1955) Treatment of ocular hypertension by adrenalin and diverse sympathomimetic amines *Amer J Ophthal 40* 666—672

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EFFECT OF CYCLOPENTOLATE ON THE AQUEOUS DYNAMICS IN INCIPIENT OR SUSPECTED OPEN ANGLE GLAUCOMA

BY

OLAVI VALLE

The effect of topically instilled cyclopentolate on aqueous dynamics was studied in 260 eyes with incipient previously untreated or suspected open angle glaucoma Parasympatholytics are known to cause significant rises in intraocular pressure in some patients with open angle glaucoma (responders) even though the chamber angles are definitely open The changes in aqueous dynamics during the cyclo pentolate provocation test (CPT) especially the differences between responders and non responders were studied to investigate the mechanism of the rise in intraocular pressure in the responders

Aqueous outflow and inflow decreased in all the groups of patients studied The changes were fairly small numerically but highly significant statistically The significant rises in intraocular pressure in responders during CPT are attributed primarily to the difference in the changes in aqueous inflow between the responders and the non responders At the same time outflow decreased fairly evenly in all the groups Outflow decreased most in the responders (by an average of 20 %) but the difference from the non responders was not statistically significant

Key words aqueous dynamics — cyclopentolate — mydriasis provocation test — open angle glaucoma — suspicion of open angle glaucoma

Several studies have dealt with the effect of different mydriatics on tonograph values in eyes with open angle glaucoma Sympathomimetics do not apparently change the aqueous dynamics of healthy persons without glaucoma (Lee 1958 Becker & *al* 1959) though parasympatholytics may slightly decrease the average c value of healthy subjects even when no significant rise in intraocular pressure occurs (Christensen & Pearce 1963 Makabe 1968)

Using the mydriasis test Galin (1961) established tonographically a distinct weakening of outflow in eight selected patients who had a significant rise of intraocular pressure in the test with cyclopentolate Some of the patients had open angle glaucoma but the others did not

Using different mydriatics Makabe (1969 a 1970) observed an average decline in the c value of 21—31 % during the mydriasis provocation test (MPT) in new previously untreated patients with open-angle glaucoma *Patients with open-angle glaucoma under concurrent miotic therapy* showed tonographically an even more distinct decrease in the c value and often a simultaneous rise of intraocular pressure during the MPT with parasympatholytics (Schimek & Lieberman 1961 Christensen & Pearce 1963 Smeral & al 1964 Makabe 1969 b)

Although several authors have reported concomitant increased resistance to aqueous outflow and intraocular pressure rises the fundamental mechanism for the rise in pressure in open-angle glaucoma has not been fully explained

This paper is part of a project to study the effect of 1 % cyclopentolate on intraocular pressure in patients with incipient previously untreated or suspected open angle glaucoma An additional object was to throw light on the mechanism of the rise in pressure itself especially in patients with a positive cyclopentolate response The effect of the cyclopentolate provocation test (CPT) on aqueous dynamics in these patients was examined A detailed report of the whole project comprising the material methods criteria and other results will be published separately in *Acta Ophthalmologica*

Patients and methods

The present study used data obtained in another one using 260 eyes for which technically successful tonography curves had been obtained on both occasions All the patients were examined at the Eye Department of the Central Hospital of Kotka They were subjected to a 3-day glaucoma investigation programme which included the following examinations determination of intraocular pressure (applanation and Schiotz) 3-day pressure curve visual fields (Goldmann) water-

drinking test gonioscopy (Goldmann) Only wide angle eyes (Gorin & Posner 1968) were included in the series that is patients whose trabecular zone as a whole and a part of the ciliary body were visible Gonioscopy was repeated during CPT if a significant rise in intraocular pressure was observed to ensure that the chamber angles were open also during CPT

MPT was performed by instilling a drop of 1 % cyclopentolate (1 % Oftan Syklo® Star) twice in both eyes with an interval of 15 min between instillations Intraocular pressure was controlled at 30 min intervals for at least 3 hours from the start of the test

Tonography was performed for the first time on the first examination day at 14 00—15 00 hours and for the second time two days later at the same time during CPT 1½—2 hours after the start of the test The tonography values are thus comparable with those recorded two days earlier for the same patients at the same time Tonography was always carried out by the same trained person The apparatus used was a V Mueller model TRLH inkless Nuvistor Tonographer The results were calculated from Friedenwald s 1955 calibration tables (Moses & Becker 1958) The 4 min tonography was performed in detail as described by Garner (1965)

The P_0 C P_0/C and F values for each eye were calculated separately from tonography curves recorded before and during CPT

Flow (F) was calculated from the formula $F = C (P_0 - P_v)$ µl/min Episcleral venous pressure (Pv) was assumed to be a constant 10 mmHg throughout (Becker & al 1956)

Patients were divided into the following groups on the basis of the response to cyclopentolate *Responders* (CR+) positive response to cyclopentolate rise of intraocular pressure ≥ 8 mm Hg *Borderline cases* (CR±) rise of intraocular pressure 5—7 mm Hg *Non responders* (CR—) negative response to cyclopentolate rise of intraocular pressure ≤ 4 mm Hg In addition changes in the aqueous dynamics were studied in the CR— and CR ± groups separately in eyes with open angle glaucoma (Group I) and eyes with suspected open angle glaucoma (Group II)

No inter-group differences in rigidity were seen The mean rigidity coefficient was normal (0 022)

Tonography in itself and also calculation of aqueous inflow and outflow contain many sources of error (Saeteren 1960 Barany 1963) Nevertheless so far it is the most useful clinical method available for studying aqueous dynamics

Student s t test was used for statistical analysis of the results

Results

Tonography showed impairment of aqueous outflow during CPT in all the groups (Table I) The mean change in the c value in the individual groups was small the most distinct change being seen in responders whose c value declined by an average of 20 % Nevertheless the difference in the outflow change between responders (CR+) and non responders (CR—) was not statistically significant ($p > 0\ 05$) Moreover

Table I

Effect of cyclopentolate provocation test (CPT) on the aqueous outflow (C) values in the different groups of patients studied (?60 eyes) Tonography was performed two days before the test and again during CPT 1 ½—2 hours after its start The table gives the mean c values (μl/min/mm Hg) and their changes (±S D) during CPT Group I eyes with recently diagnosed open angle glaucoma Group II eyes suspected of having open angle glaucoma. Responders (CR +) positive cyclopentolate response rise of IOP ≧ 8 mm Hg Borderline (CR ±) rise of IOP 5—7 mm Hg Non responders (CR—) negative cyclopentolate response rise of IOP ≦ 4 mm Hg

	Responders	Borderline		Non responders	
	Group I + II	Group I	Group II	Group I	Group II
Before CPT	0 15±0 06	0 15±0 05	0 22±0 05	0 16±0 05	0 23±0 06
During CPT	0 12±0 04	0 13±0 04	0 20±0 04	0 15±0 05	0 21±0 05
Change	—0 03±0 05	—0 02±0 04	—0 02±0 05	—0 01±0 05	—0 02±0 06
%	—20 0	—13 3	—9 1	—6 3	—8 7
No of eyes	19	27	20	84	110

there was no significant difference in the changes in the c values between the groups with glaucoma and suspected of having glaucoma

Individual differences in the changes in the outflow values were great The changes in each eye in the responder group are shown in Fig 1

The P_o/C values were raised in all groups The change was slight for the non responders and the borderline group (Table II) During CPT responders showed a more distinct change in the P_o/C value than in the c value P_o/C rose in responders by an average of 41 5 % The change in P /C between groups CR+ and CR— was statistically significant ($p < 0 01$) No significant difference was found in the P_o/C change between the glaucoma group and the group suspected of having glaucoma

The aqueous inflow (F) values before and during CPT in the different groups are shown in Table III Inflow increased slightly during CPT only in the responders It decreased in all the other groups most of all in the non responders with suspected glaucoma The difference in the change of inflow between the responders and non-responders was statistically significant ($p < 0 01$) Within the non-responders group the difference in the change in inflow between the glaucoma group and suspected glaucoma group was highly significant ($p < 0 001$) No significant difference was seen in the CR± group between the glaucomatous eyes and eyes suspected of having glaucoma

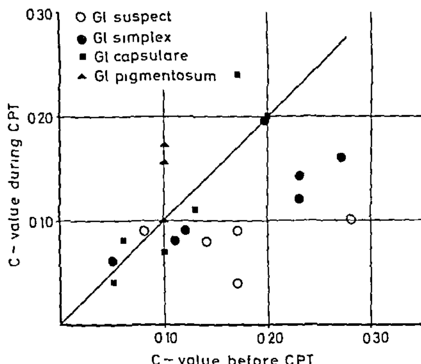


Fig 1
Distribution of change in outflow coefficient in 21 eyes with positive cyclopentolate provocation test

Table II
Changes in P_0/C in the different groups of the patients studied (260 eyes) during the cyclopentolate provocation test (CPT) Tonography was performed two days before the test and again during CPT 1½—2 hours after its start The table gives the mean P_0/C values and their changes (±S D) during CPT Group I eyes with recently diagnosed open angle glaucoma Group II eyes suspected of having open angle glaucoma Responders positive cyclopentolate response rise of IOP ≥ 8 mm Hg Borderline rise of IOP 5—7 mm Hg Non responders negative cyclopentolate response rise of IOP ≤ 4 mm Hg

	Responders	Borderline		Non responders	
	Group I + II	Group I	Group II	Group I	Group II
Before CPT	217±106	247±105	107±28	181±69	100±?9
During CPT	307±135	266±109	113±30	186±85	101±33
Change	+ 90±116	+ 19± 88	+ 6±30	+ 5±66	+ 1±30
%	+ 41 5	+ 7 6	+ 5 6	+ 2 8	+ 1 0
No of eyes	19	27	20	84	110

Table III

Effect of the cyclopentolate provocation test (CPT) on the aqueous inflow (F) values in the different groups of patients studied (260 eyes) Tonography was performed two days before the test and again during CPT 1 ½—2 hours after its start The table gives the mean F values (μl/min) and their changes (±S D) during CPT Group I eyes with recently diagnosed open angle glau coma Group II eyes suspected of having open angle glaucoma Responders (CR+) positive cyclopentolate respon e rise of IOP ≥ 8 mm Hg Borderline (CR±) rise of IOP 5—7 mm Hg Non-responders (CR—) negative cyclopentolate response rise of IOP ≤ 4 mm Hg

	Responders	Borderline		Non responders	
	Group I + II	Group I	Group II	Group I	Group II
Before CPT	2 1±1 4	2 3±0 7	2 6±0 9	2 2±0 9	2 5±0 9
During CPT	2 3±1 4	2 2±0 8	2 3±0 9	2 1±0 8	1 9±0 8
Change	+ 0.2±0 8	—0 1±0 8	—0 3±1.2	—0 1±0 8	—0 6±0 9
%	+ 9 5	— 4 3	— 11 5	— 4 5	— 24 0
No of eyes	19	27	20	84	110

Table IV

Changes (mean ± S D) in aqueous dynamics (C P_o/C and F) in a total of 260 eyes during the cyclopentolate provocation test (CPT)

	C μl/min/mm Hg	P /C	F μl/min
Before CPT	0 20±0 07	151± 82	2 4±0 9
During CPT	0 18±0 06	162±100	2 1±0 9
Change	— 0 02±0 05	+ 11± 64	— 0 3±0 9
%	— 10 0	+ 7 3	— 12 5

The difference is significant at P < 0 001
The difference is significant at P < 0 05

On the whole cyclopentolate caused numerically fairly small changes in aqueous dynamics in all the groups of patients studied (Table IV) both outflow and inflow decreased and P /C rose Nevertheless statistically the changes were highly significant for outflow and inflow (p < 0 001) and almost significant for P_o/C (p < 0 05)

The mean P_o in all the patients studied (260 eyes) before CPT was 23 0 ± 4 3 mmHg The changes in intraocular pressure during CPT will be published separately in *Acta Ophthalmologica*

Discussion

Outflow values decreased with cyclopentolate in all the groups of patients studied Several other workers have obtained similar results with cyclopentolate and other parasympatholytics (Christensen & Pearce 1963 Barany & Christensen 1967 Makabe 1969 a 1970) In experiments on rabbits cyclopentolate and homatropine used topically were found also to provoke opposite changes in aqueous dynamics (Uusitalo 1972) A decrease in outflow values during CPT especially in eyes with a significantly raised intraocular pressure (i e in responders) has been reported (Galin 1961 Schimek & Lieberman 1961) Responders were of special interest in the present work although the outflow values in them showed the greatest decrease no statistically significant difference was found in the change in values between the responders and non responders (Table I)

By contrast there was a significant difference ($p < 0\ 01$) in the average change in inflow between the responders and non-responders (Table III) During CPT inflow decreased in the other groups but increased slightly in responders Since outflow was already impaired initially it declined further with a resulting rise in intraocular pressure In most patients studied inflow decreased more distinctly than outflow and the intraocular pressure was slightly reduced during CPT

When evaluating the inflow results it must be remembered that they were calculated on the assumption that episcleral venous pressure (P_v) was a constant 10 mmHg It is not known how cyclopentolate affected P_v

The exact mechanism of the rise in intraocular pressure in responders during CPT must remain a matter for speculation Changes in aqueous dynamics are associated essentially with the mechanism established in the present study Cyclopentolate and other cycloplegics probably act directly on the ciliary muscle Thus probably there is a causal relationship between paresis of accommodation and a rise of intraocular pressure (Harris 1968 Harris & Galin 1969) The ciliary muscle obviously also regulates intraocular pressure as Fortin reported as long ago as 1929 Armaly s (1958) studies substantiate this hypothesis He observed tonographically that accommodation improves outflow with a concomitant decrease in intraocular pressure to 1—6 mmHg

In his monograph on the mechanism regulating intraocular pressure Uusitalo (1972) concludes »Although the mechanism by which the parasympatholytic and -mimetic drugs influence intraocular fluid dynamics remains open it can be said that inflow seems to play a more important role than outflow »

The results of the present clinical study agree with this conclusion The significant rises in intraocular pressure shown in responders during CPT are accounted for chiefly by the significant difference ($p < 0.01$) in the changes in aqueous inflow between the responders and non-responders (Table III) Outflow decreased concurrently at a fairly even rate in all the groups (Table I) As individual variations were great outflow decreased so much in some cases that by itself it can explain the significant rise in intraocular pressure in these eyes during CPT

References

Armaly M F & Burian H M (1958) Changes in the tonogram during accomodation *Arch. Ophthal 60* 60—69

Barany E H (1963) A mathematical formulation of intraocular pressure as dependent on secretion ultrafiltration bulk outflow and osmotic reabsorbtion of fluid *Invest Ophthal 2* 584—590

Barany E & Christensen R E (1967) Cycloplegia and outflow resistance *Arch Ophthal 77* 757—760

Becker B Gage T Kolker A. E & Gay A. J (1959) The effect of phenylephrine hydrochloride on the miotic treated eye *Amer J Ophthal 48* 313—321

Becker B Keskey G P & Christensen R E (1956) Hypersecretion glaucoma *Arch Ophthal 56* 180—187

Christensen R E & Pearce I (1963) Homatropine hydrobromide *Arch Ophthal 70* 376—380

Fortin E P (1929 a) Ciliarmuskel und Glaukom *Arch Oftalm B Aires 4* 369—373 (Spanish) Ref Zbl Ophthal (1930) 22 368—369

Fortin E P (1929 b) Schlemmscher Kanal und Ligamentum pectineum *Arch Oftalm B Aires 4* 454—459 (Spanish) Ref Zbl Ophthal (1930) 22 419

Galin M A (1961) The mydriasis provocative test *Arch Ophthal 66* 353—355

Garner L L (1965) *Tonography and the galucomas* Thomas Springfield, Ill

Gorin G & Posner A (1968) *Slit lamp gonioscopy* 3rd ed Williams & Wilkins Baltimore

Harris L (1968) Cycloplegic induced intraocular pressure elevations *Arch Ophthal 79* 242—246

Harris L S & Galin M A (1969) Cycloplegic provocative testing *Arch Ophthal 81* 544—547

Lee P F (1958) The influence of epinephrine and phenylephrine on intraocular pressure *Arch Ophthal 60* 863—867

Makabe R (1968) Tonographie unter Mydriasis *Klin Mbl Augenheilk 15?* 37—45

Makabe R (1969 a) Vergleichende Untersuchungen uber den Einfluss verschiedener Mydriatica auf die Tonographie *Klin Mbl Augenheilk 154* 217—2 0

Makabe R (1969 b) Mydriasis-Tonographie unter Miotikatherapie *Klin Mbl Augenheilk 155* 394—400

Makabe R (1970) Antagonistische Wirkung von Mydriatika und Miotika auf den Kammerwasserabflusswiderstand *Klin Mbl Augenheilk 157* 30—38

Moses R A & Becker B (1958) Clinical tonography The scleral rigidity correction *Amer J Ophthal 45* 196—208
Saeteren T (1960) The tonographic method for measuring aqueous flow *Acta ophthal (Kbh) 38* 511—523
Schimek R A & Lieberman W J (1961) The influence of Cyclogyl® and Neosynephrine® on tonographic studies of miotic control in open angle glaucoma *Amer J Ophthal 51* 781—784
Smeral L Rehak S & Juran J (1964) Kombination der Tonographie mit Belastungsproben zur Fruhdiagnostik des Glaukoms *Čs Oftal 20* 289—293 (Czechish) Ref Zbl Ophthal (1965) 95 114
Uusitalo R (1972) Studies on the mechanism regulating the intraocular pressure in the rabbit *Acta Instituti Anatomici Universitatis Helsinkiensis* Suppl 3 Thesis Helsinki

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STUDIES ON THE ULTRASTRUCTURE OF THE BLOOD AQUEOUS BARRIER IN THE RABBIT

BY

RISTO UUSITALO JOHAN STJERNSCHANTZ and ARTO PALKAMA

In the search for the structures of ciliary body which form the barrier separating the aqueous from the stroma of the ciliary processes the ciliary epithelium has been thought to be the most important (Cole 1966 Holland 1966 Vegge 1971) The most simple way of breaking down the blood-aqueous barrier is by paracentesis This gives rise to the formation of a plasmoid aqueous and also morphological changes in certain regions of the ciliary epithelium (Kozart 1968) A protein rich aqueous humour may also be produced by parasympathetic stimulation (Stjernschantz *et al* 1973)

We have reviewed some recent experiments performed to study the characteristics of the blood aqueous barrier They showed that in rabbits the passage of a protein molecule (horseradish peroxidase) through the intercellular spaces of the nonpigment epithelium in the ciliary body is blocked In the iris the barrier to horseradish peroxidase (HRP) is formed by the vascular endothelium We have also shown that parasympa thetic stimulation of the rabbit eye produces remarkable morphological changes in the ciliary epithelium and that during stimulation communicating channels exist between the apical intercellular space and the posterior chamber

Material and methods

To localize the blood aqueous barrier in the ciliary body and iris a protein tracer (HRP) was administered to anaesthetized rabbits by intravenous injection The eyes were enucleated between 6 and 9 min after the peroxidase injection Its distribution in the different regions of the ciliary body and in the iris was studied using the method favoured by Karnovsky (Graham and Karnovsky 1966 Karnovsky 1967) In some rabbits the parasympathetic (oculomotor) nerve was stimulated electrically for about 15 min (Uusitalo 1972) before the animals were injected In the stimulated rabbits both eyes were also enucleated between 6 and 9 min after the HRP injection so that the total stimulation time was about 20—25 min

Results and discussion

Barrier in the ciliary body

In the various regions of the ciliary body exogenous peroxidase was localized in the lumen of the vessels the vesicles throughout the cytoplasm and the intercellular clefts between the endothelial cells Peroxidase easily penetrated the stroma as well as the basement membrane surrounding the vessels and pigment cells and the intercellular spaces between the pigment cells (Fig 1) In the iridial processes no reaction product penetrated the lateral intercellular space of the nonpigment epithelium An obvious difference between the iridial and other processes of the ciliary body was that in some places in the ciliary processes and pars plana electron-opaque material was seen near the basal pole of the nonpigment epithelium

These findings indicate that to a large degree horseradish peroxidase is prevented from traversing the nonpigment epithelium in the ciliary body This epithelium could therefore be characterized as a »barrier» While other proteins and large molecules would probably be similarly impeded at this barrier smaller substances might not Moreover the blood aqueous barrier is more impermeable in the iridial processes than in the ciliary processes and pars plana

Barrier in the Iris

In the iris exogenous peroxidase was localized in the lumina of the blood vessels and in some micropinocytotic vesicles within the endothelial cells (Fig 2) None was found beyond the vascular endothelium The micropinocytotic vesicles were few and did not appear to transport peroxidase

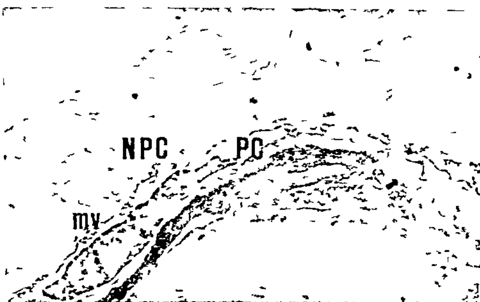


Fig 1

Intravenously administered peroxidase is localized in the electron micrograph by a dense reaction product Peroxidase penetrates readily through the inter cellular spaces of pigment cells (PC) and may be seen in the apical membranes of pigment and nonpigment cells (NPC) Stained microvillous projections (mv) in the ciliary channel between pigment and nonpigment cells of iridal process (X 5800)

while the tight junctions between the endothelial cells probably prevented its intercellular passage These findings indicate the presence of a barrier» at the endothelium of vessels in the iris

Parasympathetic stimulation

In all the stimulated eyes remarkable morphological changes were observed in the pars plana ciliary and iridial processes of the ciliary body These changes were not observed in the control eye or in the iris of the stimulated eye Intravenously injected protein tracer (HRP) freely penetrated both layers of the ciliary epithelium again a finding not seen in the control eyes In the iris no extravascular HRP was detected in the control or stimulated eyes

The changes in ultrastructure of the different regions of the ciliary epithelium after the stimulation varied somewhat Usually the intercel-

lular spaces among the cells of the nonpigment epithelium were dilated and the cells aquired very irregular shapes In some stimulated eyes the pigment epithelium was affected more markedly than the nonpigment epithelium The changes were not seen in all regions of the ciliary body

Stimulation produced saccular dilatations filled with a finely granular material between the pigment cells of the ciliary epithelium (Fig 3) The large intercellular cavities of the pigment epithelium were apparently bounded by the cytoplasm of the pigment cells and blocked by the junctional complexes connecting the apical side of the lateral surfaces of adjacent pigment cells The intercellular spaces between the apices of the pigment and nonpigment epithelium were also interrupted by the dilatations containing a finely granular material The dilatations of the lateral intercellular clefts and surface infoldings of the nonpigment epithelium were prominent (Fig 4) These dilatations were devoid of



Fig 2

Peroxidase is localized in the lumen of the iris vessel The micropinocytotic vesicles within the endothelial cell are also filled (arrow) (X 8700)

Fig 4

Electron micrograph of the nonpigment epithelium from a ciliary process after stimulation Note prominent dilatations of the lateral intercellular space and the surface infoldings of the nonpigment epithelial cells (X 10 200)

Fig 3

Electron micrograph of the pigment and nonpigment epithelium from an iridial process after parasympathetic stimulation The structure of the nonpigment epithelium is normal The structure of the pigment epithelium has been altered by the appearance of widely dilated intercellular spaces surrounded by strands of pigment epithelial cytoplasm Note the absence of reaction product (X 3700)

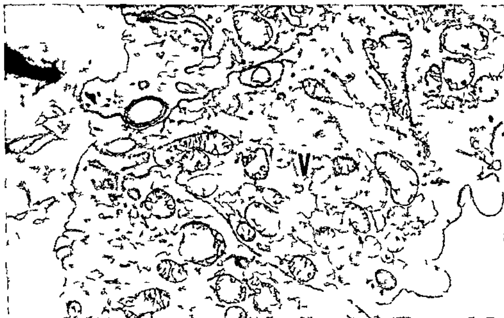


Fig 5
The nonpigment epithelium fixed in 3 % $KMNO_4$ from a ciliary process after stimulation Note the disappearance of the interdigitations between adjacent cells The basal surface of the nonpigment epithelium is very irregular and contains vesicles (V) of different size (X 11 600)

any electron dense material The junctional complex at the apical extension of the intercellular space seemed to be unaffected In one stimulated eye stretching of the nonpigment cells associated with the disappearance of the interdigitations between adjacent cells was also observed This is seen in Fig 5 where the basal surface of the nonpigment epithelium is very irregular and contains vesicles of different size

In the stimulated eyes the reaction product was difficult to detect anywhere in the ciliary body although the iridial capillaries were filled with it In the regions where marked morphological changes were observed the HRP had totally disappeared after stimulation (Fig 3) while in other regions some staining was seen between the apical membranes of the epithelial cells

The nonpigment and pigment epithelial cells undergo morphological changes after stimulation which evidently causes the HRP to pass freely into the posterior chamber Although the reaction product was not seen in the basal pole of the nonpigment cells or in its lateral intercellular

spaces evidently during stimulation communicating channels exist between the apical intercellular space and the posterior chamber The junctional complex at the apical extension of the intercellular space seemed to be unaffected This implies that some barrier persisted which impeded the passage of protein from the stroma to the posterior chamber Because the HRP disappeared from the ciliary body so rapidly during stimulation most probably the permeability of this junction changed The other possibility is for its passage through the nonpigment epithelium e g as pinocytosis This is however improbable because no vesicles containing reaction product were seen in the basal pole of these cells

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References

Cole D F (1966) Aqueous humour formation *Docum ophthal 21* 116

Graham R C & Karnovsky M J (1966) The early stages of absorption of injected horseradish peroxidase in the proximal tubules of mouse kidney ultrastructural cytochemistry by a new technique *J Histochem Cytochem 16* 291

Holland M G (1966) In vitro studies of ciliary body ion transport hypothermia and the electrophysiologic phenomena of active transport *Amer J Ophthalmol 6?* 1128

Karnovsky M J (1967) The ultrastructural basis of capillary permeability Studies with peroxidase as a tracer *J Cell Biol 35* 213

Kozart D M (1968) Light and electron microscopic study of regional differences in the proce ses of the ciliary body in the rabbit *Invest Ophthal 7* 15

Stjernschantz J Palkama A Uusitalo R & Renkonen O V (1974) Aspects of the blood aqueous barrier with special reference to the penetration of antibiotics *Acta ophthal* (Kbh) Suppl *123* 69—74

Uusitalo R (1972) Effect of sympathetic and parasympathetic stimulation on the secretion and outflow of aqueous humour in the rabbit eye *Acta physiol scand 86* 315

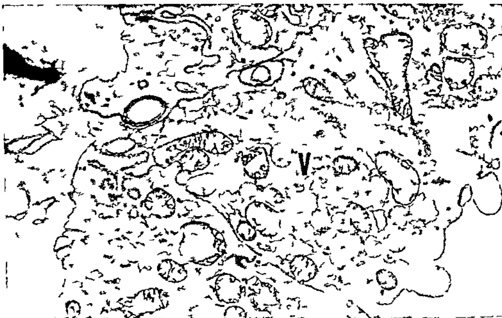


Fig 5

The nonpigment epithelium fixed in 3 % $KMNO_4$ from a ciliary process after stimulation Note the disappearance of the interdigitations between adjacent cells The basal surface of the nonpigment epithelium is very irregular and contains vesicles (V) of different size (X 11 600)

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ASPECTS OF THE BLOOD AQUEOUS BARRIER WITH SPECIAL REFERENCE TO THE PENETRATION OF ANTIBIOTICS

BY

JOHAN STJERNSCHANTZ ARTO PALKAMA RISTO UUSITALO and OLLI VEIKKO RENKONEN

The penetration of benzylpenicillin sodium and doxycycline hydro chloride into the aqueous humour of the rabbit eye after intravenous injection was studied under normal conditions and during parasympathetic stimulation The antibiotic concentrations were measured microbiologically

The normal penetration of doxycycline hydrochloride was better than that of benzylpenicillin sodium The half life of doxycycline hydrochloride in the plasma was also considerably longer than that of benzylpenicillin sodium

With parasympathetic stimulation the concentration of the both drugs in the aqueous humour of the stimulated eye increased significantly (about twice) Simultaneously the protein concentration of the aqueous humour in the stimulated eye increased highly significantly compared with the normal eye The blood pressure measured during stimulation was not appreciably changed

Most antibiotics enter the intraocular space with extreme difficulty and only in small quantities Nevertheless various structures of the eye differ considerably from one another in this respect (Bleeker *et al* 1968 Bloome *et al* 1970 Furgiuele 1964 Salminen 1973) The blood aqueous barrier prevents the normal entry of antibiotics into the aqueous humour

Vegge T (1971) An epithelial blood aqueous barrier to horseradish peroxidase in the ciliary processes of the vervet monkey (Cercopithecus aethiops) Z Zellforsch 114 309

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parasympathetic stimulation The current output varied from 2 5 to 5 0 mA The duration of the impulse was 0 8 msec and the frequency 44/sec

The antibiotic assays were performed microbiologically The benzylpenicillin sodium concentration in plasma and aqueous humour samples was measured by the method of Bennett *et al* 1966 The holes were punched in Demain s medium normally used in PKU (phenylketonuria) studies The test organism used was *Bacillus subtilis* (ATCC 6051) The standards were prepared in human plasma Doxycycline hydrochloride concentrations were estimated by the same method The test strain used was *Bacillus cereus* (ATCC 9634) the medium being Difco penassay seed agar

The results are given as arithmetical means ± standard errors of the means The t test between two means (De Jonge 1964) was used to evaluate statistical significances

Results

The mean penicillin (benzylpenicillin sodium) concentration in plasma one minute after its injection was 4714 3 ± 832 2 i u /ml The half life of penicillin was about 16 min calculated from the one-minute value The corresponding values for doxycycline (doxycycline hydrochloride) were 14 4 ± 1 3 μg/ml and 27 min

In the aqueous humour of normal eyes the penicillin concentration was highest 30 min after the injection being 95 0 ± 36 6 i u /ml Thereafter it decreased relatively rapidly The highest doxycycline concentration 0 59 ± 0 15 μg/ml was found 60 min after the injection It remained at that level at least for one hr Corresponding ratio-values (aqueous humour/plasma concentration ratio) calculated by measuring aqueous humour concentration at 10 30 60 and 120 min after the injection and the plasma concentration one minute (maximal level) after the injection showed that the penetration of doxycycline into the aqueous humour of normal eyes was somewhat superior to that of penicillin

In the parasympathetically stimulated eyes 30 min after the injection the mean penicillin concentration was increased to 280 0 ±63 5 i u./ml In the control eyes of the stimulated animals it was 162 5 ±54 8 i u./ml The corresponding value of the normal group was 95 0 ±36 6 i u /ml In the doxycycline group the values at 30 min were 0 64 ± 0 01 μg/ml in the stimulated eyes and 0 35 ± 0 02 μg/ml in the control eyes of the same animals The difference between the stimulated eyes and control eyes of the doxycycline group was significant ($p < 0\ 01$) The doxycycline concentration of the corresponding normal eyes was 0 45 ± 0 17 μg/ml The ratio-value (see above) of penicillin at 30 min was 0 05 ± 0 00 in the parasym-

pathetically stimulated eyes and 0 03 ± 0 01 in the control eyes of the same animals This difference was significant (p < 0 01) The corresponding ratios in the doxycycline group were 0 06 ± 0 01 in the stimulated eyes and 0 03 ± 0 00 in the control eyes of the same animals This difference was almost significant (p < 0 05) (Table I)

The protein content of the normal aqueous humour was 65 4 ± 6 7 mg/100 ml The corresponding concentration of plasma was 5058 2 ± 111 0 mg/100 ml In the parasympathetically stimulated eyes the mean protein content was 186 8 ± 25 5 mg/100 ml and in the contralateral eyes it was 112 2 ± 19 9 mg/100 ml The difference between the mean protein content of the parasympathetically stimulated eyes and the normal eyes was highly significant (p < 0 001) The difference between the stimulated and the contralateral eyes was almost significant (p < 0 05) The difference between the control eyes of stimulated animals and normal eyes was almost significant (p < 0 05) too (Table II)

The mean arterial blood pressure measured from the femoral artery was 95 0 ± 3 9 mmHg

Table I

Effect of parasympathetic stimulation on protein and doxycycline concentration of the rabbit aqueous humour Standard errors are those of the mean

	10 min after injection		30 min after injection	
	Doxyc conc µg/ml	Prot conc mg/100 ml	Doxyc conc µg/ml	Prot conc mg/100 ml
Control eyes	0 23±0 05	109 9±22 0	0 35±0 02	114 4±37 0
Stimulated eyes	0 55±0 10	165 6± 9 4	0 64±0 07	208 0±51 4

Table II

Effect of parasympathetic stimulation on protein content of the rabbit aqueous humour (mg/100 ml) in all the stimulated eyes and all the control eyes of the stimulated animals Stimulated and control eyes have been compared with normal eyes Standard errors are those of the mean

Stim eyes	Contr eyes	Norm eyes	Plasma
186 8±25 5 *	112 2±19 9 *	65 4±6 7	5 058 2±111 0

p < 0 05 p < 0 001

Discussion

The findings indicate that the penetration of doxycycline into the aqueous humour of the normal rabbit eye is somewhat superior to that of penicillin The dosage used of each drug was the same as that generally used in childhood bacterial meningitis at present and hence the aqueous humour levels of both of them were sufficient to treat most suspectible bacteria

The results of parasympathetic stimulation on aqueous humour dynamics further confirm the findings of Palkama and Uusitalo (1971) the effect on the penetrability of each drug being about the same Schach von Wittenau and Yeary (1963) stated that antibiotics with a high liposolubility e g doxycycline were particularly highly bound to plasma proteins Whether the increased antibiotic concentration of parasympathetically stimulated eyes is due to a better passage through the blood-aqueous *barrier by free antibiotic purely or also by protein bound antibiotic is hard* to answer Probably there is a correlation between the increased antibiotic concentration and the protein concentration

The blood pressure was recorded during parasympathetic stimulation The normal blood pressure measured from the femoral artery was about the same as that reported by Bill (1963 a b) It increased however especially at the beginning of stimulation but recovered relatively quickly to about the normal level (3—4 min)

Evidently this technique of stimulation is seldom absolutely unilateral but there is also a moderate increase in proteins and antibiotic concentrations of the aqueous humour in the contralateral eye This can probably be explained by the close anatomical relationship of the oculomotor (parasympathetic) nerves at the site of the stimulation

Hence our findings suggest a relation between the regulation of the blood-aqueous barrier and the parasympathetic nerve system which agrees well with earlier results of a study into the role of the parasympathetic nerve system in the regulation of the blood-aqueous barrier (Uusitalo *et al* 1973)

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References

Bennett J V Brodie J L Benner E J and Kirby W M M (1966) Simplified accurate method for antibiotic assay of clinical specimens. Appl Microbiol 14 170

Bill, A (1963 a) Blood pressure in the ciliary arteries of rabbits Exp Eye Res 2 20

Bill A (1963 b) Effects of cervical sympathetic tone on blood pressure and uveal blood flow after carotid occlusion Exp Eye Res 2 203

Bleeker G M van Haeringen N J Maas E R & Glasius E (1968) Selective properties of the vitreous barrier Exp Eye Re 7 37

Bloome M A Golden B & McKee A P (1970) Antibiotic concentration in ocular tissues Arch Ophthal 83 78

De Jonge H (1964) Inleiding tot de medische statistiek Deel 2 Verhandeling van het Nederlands Instituut voor Praeventieve Geneeskunde Leiden 486—487

Purgiuele F P (1964) New antibiotics Their intraocular penetration Amer J Ophthal 58 443

Langham M (1951) Factors affecting the penetration of antibiotics into the aqueous humour Brit J Ophthal 35 614

Lowry O H Rosebrough N J Farr A L & Randall R Y (1951) Protein measurement with the Folin phenol reagent 193 265

Nakatsue T (1971) Intraocular penetration of antibiotics into rabbit eye with purulent uveitis Acta Soc Ophthal jap 75 1231

Palkama A & Uusitalo R (1971) The significance of nervous system in the control of intraocular pressure Centrary of the Chair of Ophtalmology and Eye Hospital University of Helsinki

Papapanos G Spitzy K H & Trichtel F (1961) Über den Durchtritt von Penicillinen in das Kammerwasser und den Glaskorper des menschlichen Auges Ophthalmologica 142 519

Rowley R A & Rubin L F (1969) Penetration of penicillin into the aqueous humour of the dog Amer J vet Res 30 1945

Salminen L Jarvinen H & Toivanen P (1969 a) Distribution of tritiated benzylpenicillin in the rabbit eye Acta Ophthal 47 115

Salminen L Jarvinen H & Toivanen P (1969 b) Distribution of tritiated tetracycline in the rabbit eye Acta Ophthal 47 430

Salminen L (1973) Distribution of penicillin ampicillin cloxacillin tetracycline and doxycycline in the rabbit eye Academic dissertation University of Turku

M Schach von Wittenau and Yeary R (1963) The excretion and ditribution in body fluids of tetracyclines after intravenous administration to dogs J Pharmacol exp Ther 140 258

Uusitalo R (1972) Effect of sympathetic and parasympathetic stimulation on the secretion and outflow of aqueous humour in the rabbit eye Acta physiol scand 86 315

Uusitalo R Stjernschantz J & Palkama A (1974) Studies on the ultrastructure of the blood aqueous barrier in the rabbit Acta ophtal (Kbh) Suppl 123 61

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EFFECT OF PARACENTESIS ON OCULAR ANTIBIOTIC CONCENTRATION

BY

LOTTA SALMINEN

Anterior chamber paracentesis before an intravenous injection of antibiotics greatly increased antibiotic concentration in the anterior part of the rabbit eye

Key words antibiotics — ocular penetration — paracentesis

In this study 50 mg/kg of ampicillin or cloxacillin sodium 10 mg/kg of tetracycline hydrochloride or 5 mg/kg of doxycycline hydrochloride was injected intravenously into a total of 120 rabbits The injected antibiotics were isotopically labelled The rabbit eyes were either normal or had had their anterior chambers emptied with a paracentesis gun one to two minutes before the antibiotic injection After the antibiotic had been injected its concentration in the plasma was continuously monitored until the animal was killed at intervals of 5 to 240 minutes The eyes were promptly enucleated frozen and dissected The antibiotic concentrat on was determined by liquid scintillation counting

The least protein-bound of the penicillins ampicillin and the most lipoidsoluble of the tetracyclines doxycyline penetrated best into the avascular structures and into the extravascular compartment of the vascu-

lar structures of the normal rabbit eye In the vascular structures prolonged therapeutic concentration was obtained after intravenous injection of ampicillin cloxacillin tetracycline and doxycycline Nevertheless most of the antibiotic present in the iris-ciliary body and in the retina-choroid preparations was situated intravascularly In the aqueous humour and cornea the therapeutic concentration was shortlasting after the intravenous injection of ampicillin cloxacillin, tetracycline and doxycycline This did not occur in the lens and vitreous body

Even if there was shortage of antibiotics in the cornea aqueous humour and lens of the normal rabbit eye there was an overflow of antibiotics in the anterior parts of the punctured rabbit eye The enhanced penetration of molecules from the blood into the iris ciliary body and aqueous humour and the increased ocular blood volume caused by the puncture of the anterior chamber led to an increased concentration of antibiotic in the iris-ciliary body and secondary aqueous humour immediately after the antibiotic injection

The higher the plasma antibiotic concentration obtained after the injection the higher its concentration in the iris-ciliary body and secondary aqueous humour The high antibiotic concentration in the latter enhanced the diffusion of the drug into the cornea limbal area lens and anterior parts of the vitreous body A therapeutic concentration was obtained in all structures of the punctured rabbit eye

These results indicate that paracentesis of the anterior chamber greatly increased antibiotic penetration from the blood into the rabbit eye In human cases of bacterial endophthalmitis paracentesis of the anterior chamber may be recommended as a diagnostic procedure It might also benefit the poor penetration of antibiotics from the blood into the interior of the human eye

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OBSERVATIONS ON THE STRUCTURAL ARRANGEMENT OF THE SOMATIC SENSORY INNERVATION IN THE IRIS OF MAMMALS

BY

MATTI SAARI

Wallerian degeneration of the myelinated nerves of the iris after denervation of the ophthalmic division of the trigeminal nerve suggests that the myelinated nerves of the iris in mammals are derived from the trigeminal nerve and are sensory Thus the flat preparation method and the trypsin digestion and bleaching technique developed by the author may be used to demonstrate the somatic sensory nerves of the iris With these methods the architecture and organisation of the myelinated nerves was observed in the iris of the pig rat guinea-pig rabbit cat and human The richness and pattern of the myelinated nerves of the iris varied from species to species The myelinated nerves did not follow the iris vessels but were arranged according to the course of the connective tissue fibres of the iris

Key words iris — sensory innervation — trigeminal nerve — Wallerian degeneration

The iris is supplied by fibres from the cervical sympathetic by parasympathetic nerve fibres from the oculomotor nerve and by sensory fibres from the ophthalmic division of the trigeminal nerve With the silver impregnation technique and staining with methylene blue all the

iris nerves are stained and the autonomic and sensory nerves cannot be differentiated Adrenergic innervation of the iris can be shown by the formaldehyde-induced fluorescence technique (Falck 1962) and the specific cholinesterase in the iris can also be localized (Koelle et al 1952) This paper presents the possibility of using the flat preparation method (Saari 1970) and trypsin digestion and bleaching technique (Saari 1971 a) to demonstrate the somatic sensory nerves of the iris and describes the pattern of these nerves in the iris of different animals and man

Material and methods

The eyes of pig rat guinea pig cat and rabbit were tudied The human iris was studied in normal »eye bank» eyes

The flat preparation method (Saari 1970) and the trypsin digestion and bleaching technique (Saari 1971 a) were used to study the architecture and organi sation of the myelinated nerves of the iris The electron microscopic technique was the same as used earlier (Saari 1971 b) The method for denervation of the ophthalmic division of the trigeminal nerve has been described in detail (Saari *et al* 1973)

Results

Denervation studies

In the cat neuroparalytic keratitis appeared in the ipsilateral eye after denervation of the ophthalmic division of the trigeminal nerve Electron microscopical examination showed in the axoplasm of the myelinated nerves of the iris changes 2—3 days after denervation and fragmentation of the myelin sheaths 5 days after denervation The details of the investigation have been presented previously (Saari *et al* 1973)

The trypsin digestion and bleaching preparations showed fragmentation and decreased staining of the myelin sheaths in the guinea pig iris 5—*11 days after trigeminal denervation Finally no myelin sheaths were* visualised in the denervated iris

Architecture and organisation of the myelinated nerves of the iris in different animals and man

The architecture and organisation of the myelinated nerves of the iris have been described in the pig (Saari 1971 b) rat (Saari & Johansson 1973) quinea pig (Saari Johansson & Huhtala 1973) and cat (Saari Huhtala & Johansson 1973)

In the rabbit the long posterior ciliary nerves send a circular plexus into the ciliary body From this plexus the myelinated nerves run into the ciliary part of the iris where they anastomose and form a nervous plexus with wide meshwork In the pupillary part the myelinated nerves divide intersect and anastomose forming a nervous plexus with smaller meshwork

In the human eye the myelinated nerves run along the long posterior ciliary nerve into the ciliary body where they form a well-developed circular plexus Rarely a myelinated nerve bundle projects into the ciliary part of the iris Some radial nerve fibres are seen They reach the pupillary part and occasionally the sphincter area Usually they contain only one nerve fibre occasionally two or three Isolated circular branches may be seen The myelinated nerves do not follow the iris vessels but they may partly run in the same radial interlacing ridge

Discussion

On the basis of the denervation experiments the myelinated nerves of the iris in mammals are derived from the ophthalmic division of the trigeminal nerve and are sensory The flat preparation method (Saari 1970) and the trypsin digestion and bleaching technique (Saari 1971 a) may then be used to study the sensory innervation of the iris In electron micrographs the sensory nerves can be definitely identified so long as they have a myelin sheath (Krapp 1962)

The richness of the sensory innervation of the iris varies from species to species The pig the cat and the rabbit have a fairly rich network of myelinated nerves in the iris The pupillary part of the guinea pig iris shows a dense plexus of myelinated nerves Myelinated nerves are seen to a lesser extent in the rat iris and least frequently in the human iris where there are usually only single radial myelinated nerve fibres

The myelinated nerves show a similar organisation in the iris with circular horizontally round-oval and vertically oval pupils They are arranged according to the course of connective tissue fibres This prevents them from being broken during pupillary movements

The sensory nerves do not follow the iris vessels This agrees with the observation of Ehinger and Falck (1966) that the iris vessels are purely sympathetically innervated

References

Ehınger B & Falck B (1966) Concomıtant adrenergıc and parasympathetıc fıbres ın the rat ırıs *Acta physıol scand* 67 201—207

Falck B (1962) Observ·ıtıon on the possıbılities to the cellular localızatıon of monoamınes by a fluorescence method *Acta physıol scand* 56 Suppl *197*

Koelle G B Wolfand L Frıedenwald J S & Allen R A (1952) Localizatıon of specıfıc cholınesterase ın ocular tıssues of the cat *Amer J Ophthal 35* 1580—1584

Krapp J (1962) Elektronenmıkroskopısche Untersuchungen uber dıe Innervatıon von Irıs und Corpus cılıare der Hauskatze unter besonderer Berucksıchtıgung der Muskulatur *Z mıkr anat Forsch 68* 418—447

Saarı M (1970) Flat preparatıon method for studyıng blood vessels and myelınated nerves of the pıg ırıs *Acta ophthal (Kbh) 48* 999—1005

Saarı M (1971 a) Trypsın dıgestıon and bleachıng for studyıng the vasculature and myelın ıted nerves of the pig ırı *Acta ophthal (Kbh) 49* 16—33

Saarı M (1971 b) Myelınated nerves of the pıg ırıs *Acta ophthal (Kbh) 49* 921—937

Saarı M & Johansson G (1973) Myelinated nerves of the rat ırıs *Acta anat* (Basel) In prınt

Saari M Johansson G & Huhtala A (1973) Myelinated nerves of the guınea pıg ırıs *Ophthal Res* In prınt

Saarı M Huhtala A & Johansson G (1973) Organızatıon of the myelınated nerves ın the cat ırıs *Exp Eye Res 17* 275—279

Saarı M Kivınıemı P Johansson, G & Huhtala A (1973) Wallerıan degenera tıon of the myelınated nerves of cat ırıs after denervatıon of the ophthalmıc dıvısıon of trıgemınal nerve An electron mıcroscopıc study *Exp Eye Res 17* 281—287

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Dıscussıon

A Palkama Have you found degenerated nerve (N V) ends (receptors)?

Answer In thıs study the Wallerıan degeneratıon of the myelınated nerves of the ırıs after trıgemınal denervatıon was studıed lıght mıcroscopıcally usıng the trypsın dıgestıon and bleachıng technıque Early changes of Wallerıan degeneratıon of these nerves was followed wıth electron mıcroscope No attentıon was paıd to the degeneratıon of the sensory nerve ends ın the ırıs

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THE ULTRASTRUCTURE OF THE AGED HUMAN LENS CAPSULE

BY

JOHAN H SELAND

Will be published separately in Acta Ophthalmologica

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Department of Anatomy (Head Professor O Eranko)
University of Helsinki Finland

SODIUM POTASSIUM ACTIVATED ADENOSINE TRIPHOSPHATASE (NaK ATPase) *ACTIVITY IN THE RAT LENS*

A histochemical and biochemical study

BY

MARKKU PALVA and ARTO PALKAMA

Earlier investigations showed the close relationship between NaK-ATPase activity and the active transport system of sodium and potassium in the lens (Bonting *et al* 1963) The lens maintains a high concentration of potassium and a low concentration of sodium compared with the surrounding media the aqueous and the vitreous humors (Harris *et al* 1965) Biochemical studies have shown that active cation transport occurs almost entirely through the anterior side of the lens (Kinsey *et al* 1965) The highest concentration of NaK-ATPase activity in the lens is found in the epithelium and probably the epithelium is the site of active transport (Bonting *et al* 1963)

Nevertheless the exact localization of NaK-ATPase activity in the cells of the lens is still unresolved After the development of a specific histochemical method for this enzyme activity (so that there exists activation by sodium and potassium and inhibition by ouabain) it is now possible to demonstrate the enzyme both by light and electron microscopy (Uusitalo *et al* 1970)

The present work was designed to demonstrate histochemically the localization of NaK-ATPase activity and to characterize the biochemical properties of this enzyme in the rat lens epithelium

Material and methods

Histochemical studies Female albino rats of Sprague Dawley strain were used for histochemical demonstration of NaK-ATPase activity The animals were killed by rapid decapitation and the eyes enucleated and immersed in the fixative

Some eyes were first frozen with dry ice cut in a cryostat at 40 microns and then transferred to the fixation solution

In the preliminary experiments different fixation media were used 0 25—2 5 % glutaraldehyde or formaldehyde in Tris HCl buffer pH 7 2 or 3 5 % Ca Formol

The lenses were carefully removed through the posterior pole of the eye under a preparation microscope during fixation. The fixation time varied from 10 to 120 min After fixation the lenses were three times rinsed in cold Tris-HCl buffer at pH 7 2 for 2—24 hr

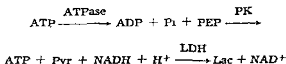
For incubation some of the whole lenses were cut with a freezing microtome at 40 microns sections but most were immersed whole in the incubation solution The incubation medium contained 0—3 mM of Ba ATP as substrate 0—6 mM of lead ($Pb(NO_3)_2$) as trapping agent 0—6 mM of magnesium 0—350 mM of sodium and 0—300 mM of potassium as activators in 0 2 M Tris HCl buffer at pH 7 8 Before incubation the pH of the solution was finally corrected to 7.2 The temperature for incubation was 37 C and its length between 10 and 120 min

After incubation the specimens were carefully washed in a sucrose-containing solution at +4 C and stained in ammonium sulphide (1 100) After brief rinsing in distilled water the free floating sections were mounted in glycerol jelly on slides

The whole lenses were first postfixed for 2 hr cut in a freezing microtome at 40 microns and then mounted

In control studies either ATP or sodium and potassium were omitted from the incubation solution Also α- or β glycerophosphates and Ba ADP were used as substrates A preincubation with ouabain before fixation was necessary to demonstrate the inhibitory effect of ouabain on NaK-ATPase

Biochemical studies Simultaneously with the histochemical analyses the kinetic properties of NaK ATPase activity were determined The lens epithelium together with the capsule were prepared and frozen in liquid nitrogen. Thereafter they were homogenized at 0 C in glass grinders with 10 volumes of 0 3 M mannitol for 1 5 min (Riley 1964) and the total ATPase and Mg ATPase activities measured at 22°C the NaK-ATPase activity was calculated as the difference between these two measurements The determinations were performed fluorometrically (Farrand s Ratio Fluorometer) according to the formula (Harkonen *et al* 197)



$$ATP \xrightarrow{ATPase} ADP + P_i + PEP \xrightarrow{PK}$$

$$ATP + Pyr + NADH + H^+ \xrightarrow{LDH} Lac + NAD^+$$

The protein was measured by the method of Lowry et al (1951)

For optimal conditions 50 mM Imidazol HCl (pH 6 5—7 3) and Tris HCl buffers (pH 7 3—8 5) were analyzed Optimal ATP Mg^{++} Na^{+} K^{+} and Mg^{++}/ATP ratio were determined as well as the inhibitory effect of ouabain and the influence of glutaraldehyde fixation.

Results

Histochemical findings The results showed that 2 5 % glutaraldehyde fixation for 30 min at +4 C was optimal Best results were found when whole lenses were subjected to fixation incubation staining postfixation and finally section cutting on a freezing microtome

An incubation solution which contained 3 mM of ATP Pb^{++} and Mg^{++} and 70 mM of Na^{+} and K^{+} yielded the most satisfactory results

In the absence of Na^{+} and K^{+} ions from the incubation medium the enzyme activity was clearly decreased (Fig 2) When the specimens were pretreated in 3×10^{-4} M ouabain solution almost total inhibition was noted (Fig 3)

In control studies α- and β-glycerophosphates gave no reaction product When ADP was used as a substrate a weak precipitate was visible in the equatorial area but this activity was not inhibited by ouabain or activated by Na^{+} or K^{+} ions

NaK-ATPase activity was localized on the epithelial cell membranes especially on the lateral parts of the cell (Fig 1) The capsule as well as the stroma showed no activity (Fig 1) In the cytoplasm of the cells no precipitation was noted

Biochemical findings The optimal pH for both the unfixed and fixed specimens was 7 7 for NaK-ATPase activity Glutaraldehyde fixation

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Fig 1

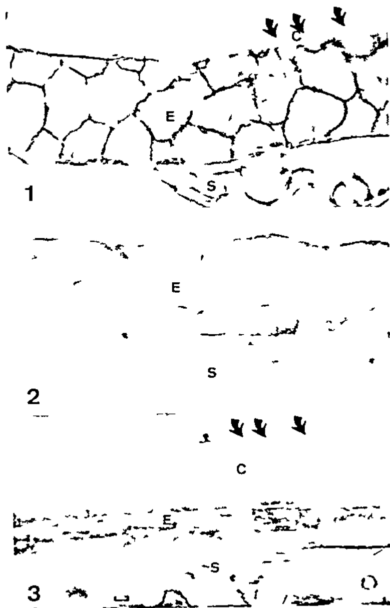
NaK-ATPase activity in the rat lens epithelium (E) Note the activity on the cell membranes Capsule (C arrows) and stroma (S) show no activity (x 420)

Fig 2

The section has been incubated as in Fig 1 but without sodium and potassium The reaction activity is clearly decreased (x 420)

Fig 3

The section has been treated as in Fig 1 except that it has been pre incubated in the presence of 3×10^{-4} M ouabain. The activity in the epithelial cells is inhibited (x 420)


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decreased the enzyme activity The optimal ATP and Mg^{++} concentrations were 2 mM and the most suitable Mg/ATP ratio 0 9—1 4

Highest NaK-ATPase activity was obtained in the presence of 70—100 mM of Na^+ and 1—30 mM of K^+ In the absence of both ions total-ATPase activity was decreased by about 30 % With 3×10^{-4} M of ouabain in the assay medium roughly the same decrease was observed

Discussion

The results showed that lens epithelium NaK-ATPase was very similar to that in the ciliary body Nevertheless the pH-optimum for NaK-ATPase differed slightly being for the lens 7 7 and for the ciliary body 8 1 Although the kinetic studies indicated that relatively low potassium concentrations (1—30 mM) yield the best activation the histochemical findings favoured a higher concentration of this ion i e 70 mM For the other components of the histochemical incubation solution the biochemical findings were similar The glutaraldehyde fixation used in the histochemical process seemed to inhibit some of the enzyme activity Thus the present results agree well with our previous ones (Palkama *et al* 1970)

NaK-ATPase activity seems to be particularly concentrated on the lateral borders of the epithelial cells These lateral parts of the cell membranes evidently form the border for the channels which may play an important part in transport of substances in and out of the lens The present morphological bio- and histochemical findings do not show the direction of this transport but provide a good basis for further studies using special electron microscopic markers

Acknowledgement

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References

Bonting S L Caravaggio L L & Hawkins N M (1963) Studies on sodium potassium activated adenosinetriphosphatase VI Its role in cation transport in the lens of cat calf and rabbit *Arch Biochem Biophys* *101* 47—55

Harris J E & Becker B (1965) Cation transport of the lens *Invest Ophthal* *4* 709—722

Harkonen M Palkama A & Uusitalo R (1972) Functional dependence of the ciliary epithelium ATPase activity and intraocular pressure on the autonomic nervous system. *Acta physiol scand 86* 3?7—341
Lowry O H Rosebrough N J Farr A L & Randall R Y (1951) Protein measurement with the Folin phenol reagent *J biol Chem 193* 265—275
Kinsey V E & Reddy D V N (1965) Studies on the crystalline lens XI The relative role of the epithelium and capsule in transport *Invest Ophthal 4* 104—116
Palkama A & Uusitalo R (1970) The histochemical demonstration of sodium potassium activated adenosine triphosphatase activity in rabbit ciliary body *Ann Med exp Fenn 48* 49—55
Riley M V (1964) The sodium potassium stimulated adenosinetriphosphatase of rabbit ciliary epithelium *Exp Eye Res 3* 76—84
Uusitalo R & Palkama A (19 0) Localization of sodium potassium stimulated adenosine triphosphatase activity in the rabbit ciliary body using light and electron microscopy *Ann Med exp Fenn 48* 84—88

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Bonting S L Caravaggio L L & Hawkins N M (1963) Studies on sodium potassium-activated adenosinetriphosphatase VI Its role in cation transport in the lens of cat calf and rabbit *Arch Biochem Biophys 101* 47—55

Harris J E & Becker B (1965) Cation transport of the lens *Invest Ophthal 4* 709—722

Material and methods

Rat corneal tissue blocks were soaked in Tris HCl buffer pH 7 2 containing 7 5 % of PVP at 22°C for 30 to 120 min Control sections were soaked in similar solu tion which however also contained 3 × 10—4M of ouabain Thereafter the tissue blocks were fixed in 2 5 % glutaraldehyde in 0 2 M Tris HCl buffer for 20 to 120 min at 4°C pH 7.2 After fixation the tissue blocks were rinsed overnight in 0 2 M Tris HCl buffer Before incubation the corneal blocks were cut at 40 *u* with a freezing microtome these sections were then immersed in the incubation solu tion The incubation was performed at 37°C according to one of the next three procedures *A* Incubation in a solution containing 0—3 0 mM of barium ATP 0—3 0 mM of lead ($Pb(NO_3)_2$) 0—3 0 mM of magnesium ($MgSO_4$) 70 mM of NaCl and KCl in 0 2 M Tris HCl buffer pH 7 2 *B* The control sections were incubated in similar solutions containing in addition 3 × 10—4M of ouabain C Another test incubation was performed as in incubation *A* but in the absence of both sodium and potassium All the sections were rinsed for 30 min and stained in 1 % ammonium sulphide solution for light microscopy

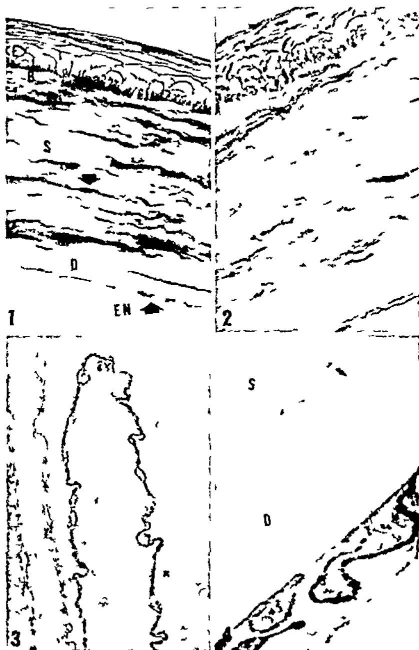
Those sections prepared for electron microscopy were postfixed after rinsing in 2 % osmium tetroxide (phosphate buffer) for 1 to 2 hr and dehydrated in alcohol The dehydrated sections were mounted in Epon Araldite cut with a LKB ultratome and viewed in a Philips EM 300

Results

Light microscopy A strong reaction was observed on the membranes of the epithelial cells (Fig 1) The most dense precipitation had occurred in the basal part of the epithelium (Fig 1) In the stroma a very strong dark brown precipitate was seen around nerve fibers (Fig 1) There was a weak reaction in the stroma in some isolated cells which may have been keratocytes Endothelial cells also showed enzyme activity on their membranes particularly in tangential preparations

Electron microscopy At high magnification epithelial cells were seen to contain a dense precipitate all over the membranes Nevertheless the most superficial epithelial cells showed no activity and neither did the basal membrane of the epithelium (Fig 3) Keratocytes showed a very weak reaction on their membranes and usually showed none at all Endothelial cells had a reaction precipitate on their lateral membranes facing the neighbouring cell (Fig 4) but none on their membranes facing Descemet s membrane or the anterior chamber of the eye

Control studies In the presence of ouabain (incubation *B)* the reac tion seen under the light microscope was clearly inhibited (Fig 2) In the absence of both sodium and potassium (incubation *C)* the reaction intensity was also decreased but not as much as in the presence of ouabain


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Discussion

The results obtained showed that corneal NaK-ATPase is histochemically similar to that found in the ciliary body (Uusitalo & Palkama 1970) It is localized on cell membranes not in organelles as has been suggested (Maeda & Sakaguchi 1965) and is mainly in the epithelium and endothelium The general pattern of the histochemical NaK-ATPase activity in the cornea closely resembles that described (Ehlers 1964 Kaye & Tice 1966 Pakarinen 1969) Nevertheless these authors could not demonstrate any inhibition by ouabain or activation by sodium and potassium and thus the precipitate obtained could not be checked for whether it represented the real enzyme activity

The precipitate indicating the localization of the enzyme is more dark (under the light microscope) or more dense (under the electron microscope) in the presence of 70 mM of sodium and potassium than in the absence of these activators Only a weak reaction product is formed in the presence of 3×10^{-4}M ouabain Taken in addition to the findings about the effects of ATP Mg^{++} and Pb^{++} these facts favour the specifity of the reaction product for NaK ATPase activity

The localization of the reaction in the basal epithelial cell membranes and in the endothelium strongly suggests the existence of active ion and water transport at these sites Whether the direction of this transport is outwards or inwards or both is still difficult to answer In the epithe-

---

Fig 1

NaK ATPase in the cornea E epithelium B Bowman s membrane S stroma D Descemet s membrane En endothelium The arrow indicates one cell of Schwann The enzyme activity is localized on the cell membranes of the epithelium Schwann s cells and endothelium (× 390)

Fig 2

Ouabain induced inhibition of NaK ATPase activity in the cornea ATPase activity is almost totally inhibited in all corneal layers (compare Fig 1) (× 390)

Fig 3

Electron micrograph showing NaK ATPase activity in the epithelium The reaction is localized purely on cell membranes (× 7850)

Fig 4

NaK ATPase activity in the corneal endothelium. Note the strong reaction on the lateral cell membranes and the absence of reaction precipitate on the membranes facing Descemet s membrane (× 7650)

lium the precipitation was localized all over the membrane and thus the question of the direction of the ion and water transport here still remains open The high activity at the lateral membranes of the endothelial cells favours a flow along the intercellular channels

Further studies are in progress to evaluate the direction of the fluid transport in the cornea by following the movements of special markers in the cornea by the electron microscope

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References

Dikstein S & Maurice D M (1972) The metabolic basis to the fluid pump in the cornea *J Physiol 221* 29—41

Ehlers N (1965) Corneal adenosine triphosphatase A histochemical investigation *Exp Eye Res 4* 48—53

Green K (1966) Dependence of corneal thickness on epithelial ion transport and stromal sodium *Amer J Physiol 217* 1169—1177

Hodson S (1971) Evidence for a bicarbonate dependent sodium pump in corneal epithelium *Exp Eye Res 11* 20—29

Kaye G I & Tice L W (1966) Studies on the cornea V electron microscopic localization of adenosine triphosphatase activity in the rabbit cornea in relation to transport *Invest Ophthal 5* 22—32

Maeda K & Sakaguchi K (1965) Studies on sodium potassium activated adenosine triphosphatase in the cornea Electron microscopic observations on the rat cornea *Jap J Ophthal 9* 195—199

Maurice D M (1972) The localization of fluid pump in the cornea *J Physiol 221* 43—54

Novikoff A P (1967) Enzyme localization with Wachstein Meisel procedures real or artifact *J Histochem Cytochem 15* 353—354

Pakarinen P (1969) Preservation of the cornea for penetrating keratoplasty An experimental study *Acta ophthal (Kbh) Suppl 106*

Palkama A & Uusitalo R (1970) The histochemical demonstration of sodium potassium activated adenosine triphosphatase activity in rabbit ciliary body A methodological study *Ann Med exp Fenn 48* 49—55

Rosenthal A S Moses H L Tice I & Ganote C E (1969) Lead ion and phosphatase histochemistry III The effects of lead and adenosine triphosphate concentration on the incorporation of phosphate into fixed tissue *J Histochem Cytochem 17* 608—612

Uusitalo R & Palkama A (1970) Localization of sodium potassium stimulated adenosine triphosphatase activity in the rabbit ciliary body using light and electron microscopy *Ann Med exp Fenn 48* 84—88

Wachstein M & Meisel E (1957) Histochemistry of hepatic phosphatase at a physiologic pH *Amer J Path 27* 13—23

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CHLOROQUINE INDUCED ULTRASTRUCTURAL CHANGES IN THE PIGMENT EPITHELIUM OF THE ALBINO RAT

BY

RITVA PERÄSALO LEENA RECHARDT and ARTO PALKAMA

Chloroquine has long been used as an antimalarial and anti-inflammatory drug but its mode of action is still unknown Its toxic side-effects especially its retinopathic action and irreversible changes produced in the retina have somewhat inhibited its therapeutic use

Several clinical studies have been reported as well as morphological changes produced experimentally with chloroquine in the eyes of animals (see e g Voipio 1966 Nylander 1966 Abraham 1970 Benson 1970 Francos 1972 Bernstein 1963 Holts 1961 Rubin 1964 Wetterholm 1964) The nature of the ultrastructural changes has so far been extremely controversial

The changes observed and the conclusions on the toxic mechanisms may be roughly divided into the following categories (see *e g* Lindquist 1972 Abraham 1970 Cohen 1965 Perez 1964) 1 The toxic effect of chloroquine is based on its being bound to melanin granules followed by the degeneration of the rods and cones 2 The primary change is an increase in the number of membrane-bound particles called myeloid bodies 3 The number of lysosomes increases during chloroquine treatment in some parts of the retina 4 Chloroquine medication leads to defective lysosomal function 5 Chloroquine interacts in several enzymatic

activities essential to the visual process such as inhibition of DNA and RNA polymerases alcoholic dehydrogenase (ADH) and succinic dehydrogenase (SDH)

Material and methods

Albino rats were treated with different doses with chloroquine phosphate intra peritoneally three times a week for various periods The doses were 12 25 and 50 mg/kg body weight The control groups received physiological saline injec tions The rats were treated from one to six months after which they were killed One group of rats was killed after a recovery period of six months i e after six months without drug treatment

The retinas were immersion fixed in Karnovsky s fixative containing both glutar and paraformaldehyde refixed in OsO_4 embedded in Epon Araldite mix ture and post stained with lead citrate and uranyl acetate Perfusion fixation was tried but this procedure did not yield any better results The specimens were viewed and photographed by using 60 kV in Philips 300 EM

Results

The pigment epithelium consists of a single row of flattened cells normally showing some characteristic features The basal surface rests on a prominent basal lamina adjacent to Bruch s membrane which separates the pigment epithelium from the choroidal tissues (Fig 1) At its base the membrane sends numerous invaginations into the pigment cell At the opposite edge long villous extensions project towards the retina The nuclei are found in the basal regions

The numerous mitochondria are placed at the base of the cell They are rod shaped in longitudinal section and round in cros section They show intramitochondrial cristae and a slightly vesicular inner structure (Fig 1)

The smooth-surfaced endoplasmic reticulum occupies much of the rather loose and tubular cytoplasm Free ribosomes are also seen (Fig 2)

At the apical parts of the cells there is a variable collection of different electron-dense bodies These bodies probably lysosomes are surrounded by a single membrane The nature of these bodies will be discussed elsewhere (Pera alo 1973) their size varies from 0 4 to 2 microns

In the control rats a larger membranous structure is seen very seldom in the normal pigment epithelial cells (Fig 2) A loosely lamellated part and a darker densely lamellated substructure attached to it are characteristic of these special structures suggesting an autophagocytotic activity Their size varies from 3 to 5 microns Some particles of lipid or lipofuscin were seen occasionally

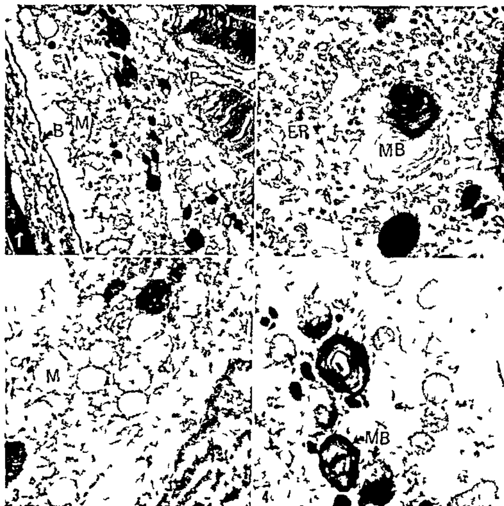


Fig 1

Pigment epithelium of control albino rat The numerous mitochondria are placed at the base of the cell Mitochondria (M) Bruch s membrane (B) villous projections (VP) (× 15 000)

Fig 2

Pigment epithelial cell of the control albino rat Myeloid body (MB) endoplasmic reticulum (ER) (× 45 000)

Fig 3

Pigment epithelium of chloroquine-treated albino rat The cytoplasm shows vacuolization and condensation of tubular reticulum and ribosomes The mitochondria are swollen (M) (× 15 000)

Fig 4

Pigment epithelial cell of chloroquine treated rat Myeloid bodies (MB) (× 15 000)

Clearcut ultrastructural changes are shown in the pigment epithelial cells after one month of chloroquine treatment with 25 or 50 mg/kg The cytoplasm shows vacuoli ation and condensation of the tubular reticulum and ribosome areas (Fig 5) The polarity of the distribution of mitochondria disappeared and the mitochondria themselves seemed swollen (Fig 3 and 4) The numb e dense bodies increased these observations need however ated statistically and this is in progress

The most promin ge is the increase of the large lamellated structures called b hors myeloid bodies In some cells they seemed to occupy l (Fig 4) In several specimens the tips of the rods were seen inv otally the into the cytoplasm of the epithelial cell The lamella of these parts of the outer segments had partially degener ked more electrondense We could not avoid suggesting that th em o be phagocytosed by the epithelial cells and that a process o truct n was possibly going on

Discussion

The ultrastruct al changes correlated with the dosage and time of the chloroquine tr atment Even after a 6 month s recovery period the changes were t e same as after an equally long period of treatment Our preliminary re ults suggest tha the ultrastructural changes are irreversible

The mecha ism and origin of myeloid bodies remain conjectural. They could be destroyed mitochondria, which most probably seem to suffer if their ultrastructure is considered A fascinating sugges on is that the outer segments are digested by the epithelial cells and the large lamellated myeloid bodies are remnants of them. Some of our ultrastructural observations would favour this suggestion. But how chloroquine promotes this destructive proces remains an open question.

Refer

Abraham R & Hendy R J (1970) Irr lysosomal damage induced by chloroquine in the retinae of pigmer [illegible] Exp mol path 1? 185—200

Bernstein H et al (1963) The ocular depo r [illegible] Invest Ophthal 2 384—39

Berson E L (19 0) Acute toxic effects of c roqu the ca [illegible] Invest Ophthal 9 618—6 8

Cohen S N & Yielding K L (1965) Spec hotom studies o the in action of chloroquine with deoxyribonucle cid. Chem [illegible] 3123—3131

Francois J *et al* (1972) Rétinopathie chloroquinique *Ophthalmologica 165* 81—99
Hobbs H E *et al* (1961) Ocular lesions after treatment with chloroquine *Brit J Ophthal 45* 284—297
Lindquist N G & Ullberg S (1972) The melanin affinity of chloroquine and chlorpromazine studies by whole body autoradiography *Acta pharmacol toxicol 31 Suppl 11*
Nylander U L F (1966) Ocular damage in chloroquine therapy *Acta ophthal (Kbh) 44* 335—347
Perez R *et al* (1964) Chloroquine binding to melanin characteristics and significance (Abstr) *Arthr Rheum 7* 337—338
Perasalo R Rechardt L & Palkama A (1974) Effect of chloroquine on acid phosphatase activity in the pigment epithelium of the retina of albino and pigmented rats *Acta ophthal Suppl 123* 99—102
Rubin M *et al* (1964) Chloroquine toxity *Second International Pharmacological Meeting 4* 467—487
Wetterholm D H *et al* (1964) Histopathology of chloroquine retinal toxity *Arch Ophthal 71* 82—87

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Discussion

S E Nilsson The melanin affinity of chloroquine has been demonstrated in vivo as well as in vitro Therefore it seems difficult to understand a damaging effect on the pigment epithelium of albino rats that lack melanin

The »myeloid bodies» that you demonstrate obviously correspond to the phagosomes described earlier by Young et al The phagosomes consist of receptor outer segment material incorporated into the pigment epithelium as a link in the process of continuous renewal of the receptor outer segments So far there is no evidence in the literature that chloroquine affects the turn over rate of the receptor outer segments Thus if your observation of an increased number of phagosomes is really related to chloroquine one would expect the mechanism to be a delayed »digestion» on the phagosomal material rather than an increased rate of incorporation of outer segment material

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EFFECT OF CHLOROQUINE ON ACID PHOSPHATASE ACTIVITY IN THE PIGMENT EPITHELIUM OF THE RETINA OF ALBINO AND PIGMENTED RATS

BY

RITVA PERÄSALO LEENA RECHARDT and ARTO PALKAMA

On the basis of the observations reported in the previous paper (Peräsalo Rechardt & Palkama 1973) on chloroquine-induced changes in the pigment epithelium of the rat eye a histochemical study using the acid phosphatase reaction was carried out Our working hypothesis was that it might indicate some changes reflecting in the lysosomal function

In general the lysosomes are considered to be storage-granule forms of organelles consisting of various hydrolytic enzymes The membranes of these pre existing lysosomes can merge into the membranes of phagosomes (see *e g* Weissman 1965) Autophagic vacuoles appear whenever a cell has to sacrifice a portion of its cytoplasm in response to a lack of nutrition or other damage to the cell as in chloroquine toxicity The lysosomes that are capable of digestion now appear filled with debris termed residual bodies The final form is called the myeloid bodies One function of chloroquine is possibly to stabilize the membranes of lysosomes *i e* to immobilize their lytic enzymatic activity (Weissman 1964)

As far as we know only one piece of research has been done using acid phosphatase to study chloroquine-treated retinas of any species Abraham & Hendy (1970) found irreversible lysosomal damage in the cytoplasm of the bipolar and ganglion cells in the rat retina but no

changes in the pigment epithelium They suggested that the lysosomal changes in the bipolar and ganglion cell layers caused the damage to the other layers of the retina and were responsible for chloroquine toxicity

Material and methods

Albino rats of the Sprague Dawley strain and pigmented rats of the Long Evans strain were treated with chloroquine 50 mg/kg body weight intraperitoneally twice a week for six months The control groups received physiological saline The acid phosphatase reaction was performed with the Gomori s lead technique (Gomori 1941) using both α and β glyserophosphate as substrates Adequate controls were made without substrate lead or with 0 01 M fluoride After 2 % paraformaldehyde 1 % glutaraldehyde fixation the retinas were washed in sucro e and incubated They were then cut into 20 or 80 μ thick sections with the freezing microtome The specimens were viewed and photographed unstained

Results

In the light microscopical sections the retinas showed a strong acid phosphatase reaction particularly in the pigment epithelium Some activity was present in the ganglion cell and the bipolar-cell layers presumably in their cytoplasm Owing to the amount of pigment no clear difference could be seen between the epithelia of the control and that of the chloroquine-treated pigmented rats

In the chloroquine-treated albino rats only a few pigment epithelia showed a stronger reaction the general impression was that on light microscopy there was no clear difference between the chloroquine treated and the control rats Certainly, no decrease of the activity was observed as has been reported for some other mammalian cells as *in vitro* chloroquine-treated leucocytes pancreatic exocrine cells and monocytes see Fedorko Hirsche & Cohn (1968)

The electron micrographs of the pigment epithelium of the control albino rat show a fine granular precipitate localized in the lysosomes marking them reliably when no poststaining is used (Fig 1) The few myeloid bodies found in the controls were surrounded by the lead reaction products (Fig 1) In addition to this the melanin granules of the pigmented control rats were surrounded by scanty precipitates This observation that melanin granules and melanosomes also show acid phosphatase activity has been reported by other authors in melanin-containing cells (Seiji & Kikuchi 1969) This observation somewhat reduces the value of acid phosphatase used as a specific marker of lysosomes

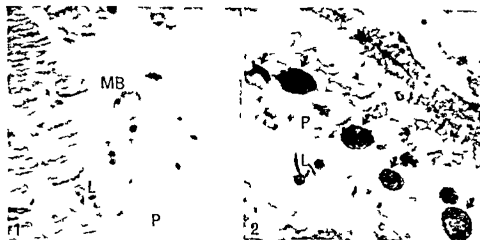


Fig 1

Electron microscopical view of a pigment epithelium cell (P) in the retina of a control albino rat A fine lead precipitate is observed in the lysosomes (L) and in a myeloid body (MB) No post staining (× 15 750)

Fig 2

Electron microscopical view of a pigment epithelium cell (P) in the retina of a chloroquine treated albino rat The lysosomes (L) appear darker than in Fig 1 as do the myeloid bodies (indicated by arrows) No post staining (× 15 750)

At the ultrastructural level the lysosomes in the chloroquine-treated rats showed stronger activity as seen in Fig 2 The more numerous myeloid bodies could be identified with lead precipitates (Fig 2) In some specimens also the Golgi lamellae showed activity Acid phosphatase activity in the Golgi lamellae has been reported in some secreting cells during activated secretion (Smith & Farquhar 1966)

The controls gave negative results as did also the nuclear and cytoplasmic membranes which have been reported to react positively in some epithelial cells (Hornova & Kukletova 1973)

Discussion

Acid phosphatases are a heterogeneous group of several hydrolytic acid phosphatases and with our technique (especially with our fixation) we are showing a particular type of enzyme We did not show any decrease of the enzyme activity which would indicate a certain stabilization of

(1963) comments upon a similar study in which the bilateral character was first recognised in only 14 out of 24 cases »Since the tumour is certainly congenital it was present in the second eye but overlooked in over 40 % of these cases»

Case series

The series was collected from two sources

Group I includes all 75 retinoblastomas registered at the Norwegian Cancer Registry since it started in 1953 Fig 1 presents the incidence per 3-year periods and Fig 2 the incidence per live newborn These figures indicate that the incidence of retinoblastoma is increasing in Norway In the period 1969—71 one retinoblastoma patient was born per 12 300 live newborns i e about 5—6 new patients per year

Group II includes all biopsy-proved retinoblastomas treated in our Eye Department during the period Jan 1950 — Jan 1973 There was 63 patients 35 males and 28 females and the bilateral incidence was 41 % i e 26 cases Two patients were mentally retarded

Relatives Seven of the bilateral cases but no unilateral ones had a family history of retinoblastoma This accords with the wellknown fact that in the second or third generation retinoblastoma usually occurs in both eyes *Among 67 brothers and sisters* one had bilateral retinoblas toma the sister to a boy with bilateral retinoblastoma born to healthy

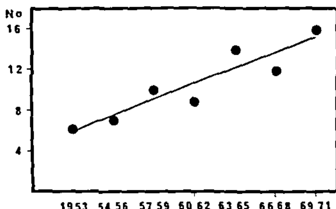


Fig 1

Distribution of patients with retinoblastoma registered at the Norwegian Cancer Registry 1953—1971 The distribution is given per 3 year periods with the exception of 1953 the first year of registration which probably also includes cases from previous years when no registration was possible

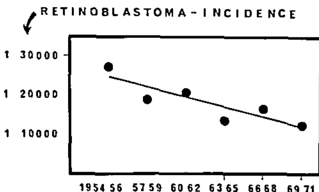


Fig 2
Incidence rate of retinoblastoma registered at the Norwegian Cancer Registry calculated per live newborn

parents Two close relatives had died one from a medulloblastoma and one from a cerebral tumour Other disorders among close relatives included mental retardation (3) congenital cataract (3) rubella syndrome (1) congenital blindness (1) and cystic kidney (1)

Age at diagnosis is presented in Fig 3 and Table I The oldest patient with bilateral retinoblastoma was 24 months while that with unilateral disease was 10 years

The retinoblastoma incidence calculated in 3-year periods is given in Fig 4 The increase is mainly caused by new unilateral cases

Bilateral retinoblastomas Of the 26 bilateral cases one was misinterpreted both clinically and histologically as »endophthalmitis Three patients were first classified as having unilateral disease the bilateral character being recognised after 3 5 and 11 months None of these patients was examined under general anesthesia under mydriasis or by the use of a binocular ophthalmoscope with scleral impression The tumour(s) in the second eye may therefore have easily been missed at the initial examination The second eye of the patient with endophthalmitis had to be removed because of retinoblastoma 2 years and 4 months later histological examination of the first and second eye verified the diagnosis of retinoblastoma

Prognosis The mortality rates are listed in Table II The four patients with unilateral tumours who died showed either secondary glaucoma (1) or extraocular tumour growth (3) at the time of enucleation Seven of the remaining 33 unilateral cases had a follow-up period of less than

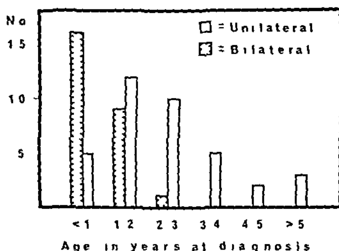


Fig 3
As a rule bilateral retinoblastoma occurs earlier that the unilateral type

2 years The five patients with bilateral disease who had both eyes removed at the first examination are all alive with follow-up periods of 3 months 3½ 6½ 7 and 7½ years

The prognosis was most unfavourable in the bilateral group when one eye was removed and the other eye treated with irradiation (X-rays Cobalt 60) or photo-coagulation or both The mortality rate of 43 % may partly be explained by the fact that some of these eyes had an extensive tumour growth and that some of the eyes received only X-rays as treatment Some of the deaths could probably have been avoided by a more careful follow up routine Previously our retinoblastoma patients were followed until the age of 5—6 years as suggested by Stallard (1955) Nevertheless the eyes treated with irradiation and/or photo coagulation showed a strong tendency for reactivation of tumor growth The longest interval between treatment and a relapse was 11 years but several cases also showed re-activation of tumour growth 4—6 years after the initial

Table I
Average age in months at first symptom and at diagnosis

Unilateral		Bilateral	
First symptom	Diagnosis	First symptom	Diagnosis
23 8	30 9	7 7	11 0

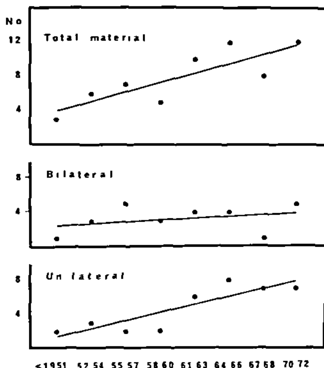


Fig 4

Age distribution of 63 patients with retinoblastoma treated at the Eye Department Rik hospitalet The increased incidence rate observed in the total series seems to be caused mainly by an increased number of unilateral case

Table II

Prognosis and mortality rates of retinoblastoma patients calculated according to treatment

	No of patients	No of deaths	Mortality rate *.
Unilateral primary enucleation	37	4	10 8
Bilateral primary enucleation of both eyes	5	0	0
Bilateral primary enucleation of one eye irradiation and/or photo-coagulation of the other eye	21	9	42 9

* Including the misdiagnosed endophthalmitis patient see text.

treatment Two of the 12 patiets still alive have follow-up periods of less than 2 years

The high mortality rate in these cases should give rise to caution in the choice of therapy A patient with retinoblastoma should never be offered treatment with irradiation or photo coagulation or both, unless there is at least a fair possibility of useful vision and the follow-up should be extensive and thorough

Comment

The results of the present study support the opinion of Reese (1963) that retinoblastoma is a congenital tumour Thus in bilateral cases the tumour is present and probably visible in both eyes at the first examination Every effort should be made to recognise the tumour in the second eye including examination with the binocular ophthalmoscope under mydriasis and scleral impression under general anesthesia

Unilateral cases in which the eye has been removed should have the other eye examined every 3rd month in the first year and every 6th month in the next year If such a two year follow-up period fails to reveal tumour in the other eye the patient is considered to be out of danger and further examination under general anaesthesia is not performed

Patients with bilateral disease in whom one eye has been removed and the other eye treated with irradiation and/or photo coagulation should be followed in the above manner if necessary under general anaesthesia every 3rd month until the age of 15 years as re-activation of tumour growth may occur at any time during this period

References

Horven E (1926) Om forekomsten og prognosen av glioma retinae *Norsk Oftalmologisk Forening* Oslo Nov 25

Jensen, O A (1965) Retinoblastoma in Denmark 1943—1958 A clinical histopathological and prognostical study *Acta ophthal (Kbh) 43* 821—840

Jerndal T Lindstedt E Svensson O & Åkerskog G (1973) Retinoblastoma in Sweden A study of 45 children with retinoblastoma with special regard to the therapeutical results *Acta ophthal (Kbh) 51* 543—550

Reese A B (1963) *Tumors of the eye* p 124 2nd ed Harper & Row New York

Stallard H B (1955) Multiple islands of retinoblastoma Incidence rate and time span of appearance *Brit J Ophthal 39* 241—243

Tarkkanen A (1973) Occurrence of mental retardation in patients with retino blastoma *Acta ophthal (Kbh) 51* 67—71

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Discussion

M Warburg The very few cases of recognised regression of retinoblastoma in the eye of a parent to a child with this tumor is probably to a considerable extent due to the lack of ophthalmoscopic examination of such parents Several families where the tumour has skipped a generation show that the mutant gene is sometimes clinically silent but the non-affected gene carriers in these families have not been examined The serious genetical prognosis in hereditary cases will no doubt excuse the spending of 30 minutes on each parent in a search for a specific clinical and genetic diagnosis

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GENETIC COUNSELLING IN RETINOBLASTOMA

BY

METTE WARBURG

An increased rate of survival of patients with retinoblastoma has resulted in an increase in the incidence of the tumour Genetic counselling of survivors with the heritable type is the duty of the ophthalmologist Risk figures are tabulated

Key words Retinoblastoma — genetics — genetic counselling — chromosomes

There are two types of retinoblastoma one is inherited as a dominant trait the other arises as a somatic mutation As there is a normal sex ratio and no increased consanguinity and as follow up of patients with bilateral retinoblastoma has shown that their offspring has a near 50 % risk of being affected (Table I) the dominant inheritance of bilateral cases is beyond question

Incidence

The incidence of retinoblastoma has increased in Europe during the last 70 years In Holland the incidence was 1 34 000 in the period 1927—29 and 1 15 000 in 1952—55 (Hemmes 1931 Schappert—Kimmijser *et al*

1966) In Finland the incidence was 1 82 000 in 1912—19 and 1 16 000 in 1960—64 (Tarkkanen *et al* 1971) Similar trends have been reported by other European authors (Francois 1968) The increase in incidence is probably particularly high in bilateral cases (Schappert—Kimmijser *et al* 1966 Bech *et al* 1965) The principal cause of this increase in the incidence is an increase in the rate of survival While at the turn of the century the survival rate was 10—30 % at the mid-century it had increased to about 50 % and now it is nearly 80 % in some centres (Table II) Survival is still somewhat lower in bilateral cases but even with a survival rate of 50 % a great many patients will be saved for future praceration

Table I
Offspring of parents with bilateral retinoblastoma (modified after Sorsby)

	Vogel 1957	Schappert Kimmijser et al 1966	Sorsby 1972	Briard Guillemot et al. 1970	Total
Parents					
Total no	2	7	10	4	23
No with healthy children	2	2	3	1	8
No with affected children	0	5	7	3	15
Offspring					
Total no	3	22	14	4	43
Healthy	3	10	6	1	20
Affected	0	12	8	3	23

Table II
Survival in unilateral and bilateral cases of retinoblastoma

	Survival		
	Unilateral	Bilateral	Year of report
Carbajal	80 %	50 %	1958
Jensen	86 %	55 %	1965
Schappert Kimmijser et al	75 %	48 %	1966
Leelawongs et al	80 %	85 %	1968
Tarkkanen et al	70 %	30 %	1971

Table IV
Genetic counselling in retinoblastoma

Inquirer	Bilateral		Unilateral	
	Familial	Sporadic	Familial	Sporadic
	Risk of offspring		Risk of offspring	
Affected	40—45 %	40—45 %	40—45 %	8 % (6—15 %) (empirical)
Parent of affected	40—45 %	5 7 % (empirical)	40—45 %	0 6 % (empirical)
Sib of affected	6 7 %	very low	6 7 %	1—1 7 % (empirical)

explained on the grounds of spontaneous regression of a tumour If such are found the parent must be considered a gene carrier and whether the first child was unilaterally or bilaterally affected they are at a 50 % risk of transmitting the mutation

If no cases are known in the family or found ophthalmoscopically in the parents, the risk of recurrence of retinoblastoma in siblings of bilaterally affected children has been found empirically to be 5 7 % (Briard-Guillemot et al 1970)

Unilaterally affected survivors of retinoblastoma have a 10—20 % risk of carrying the genetic mutation Only such carriers have the risk of transmitting the disease If another case of retinoblastoma is known in the family the prospective parent should be counselled as a case carrying the dominant gene

If the unilateral case is truly sporadic the calculated risk of affected offspring is 8 % (20 % genetic cases with 40 % risk of manifestation in the offspring) Empirically the risk is 6 6—15 % (Briard-Guillemot *et al* 1970 Nielsen *et al* 1968)

In sporadic cases whether unilateral or bilateral, the sibling of the affected person runs a very low risk of affected offspring (Table IV) Even the low figure of 7—8 % risk of having a child with a malignant tumour must be regarded as ominous All children with risk figures of this or higher levels should be given ophthalmic examinations under anaesthesia from soon after birth until the age of seven years at fixed though increasing intervals

References

Bech K & Jensen O A (1961) Bilateral retinoblastoma in Denmark 1928—1957 *Acta Ophthal (Kbh) 39* 561

Briard Guillemot M L Frezal J & Lamy M (1970) Erste Resultate einer weiteren Untersuchungsreihe uber das Retinoblastom *Mschr Kinderheilk 118* 254

Carbajal U M (1958) Observations on retinoblastoma *Amer J Ophthal 45* 391

Cumings J N & Sorsby A (1944) Unilateral and bilateral retinoblastoma A possible histological difference *Brit J Ophthal 28* 533

Francois J (1968) Heredity of malignant tumors of the eye In *Congenital anomalies of the eye* C V Mosby Co Saint Louis

Grace E Drennan J Colver D & Gordon R R (1971) The 13q deletion syndrome *J Med Genet 8* 351

Hemmes G D (1931) Untersuchung nach dem Vorkommen von Glioma retinae bei Verwandten von mit dieser Krankheit Behafteten *Klin Mbl Augenheilk 86* 331

Jensen, O A (1965) Retinoblastoma in Denmark 1943—58 A clinical histological and prognostic study *Acta Ophthal (Kbh) 43* 821

Knudson A G (1971) Mutation and cancer Statistical study of retinoblastoma *Proc nat Acad Sci (Wash) 68* 820

Leelawongs N & Regan C D J (1968) Retinoblastoma A review of ten years *Amer J Ophthal 66* 1050

Macklin M T (1959) Inheritance of retinoblastoma in Ohio *Arch Ophthal 62* 842

Morgan S S & Bair H L (1968) Hereditary retinoblastoma Report of a family with retinoblastoma occurring in three successive generations *Amer J Ophthal 65* 43

Nielsen M & Goldschmidt E (1968) Retinoblastoma among offspring of adult survivors in Denmark *Acta ophthal (Kbh) 46* 736

Schappert Kimmijser J Hemmes G D & Nijland R (1966) The heredity of retinoblastoma *Ophthalmologica 151* 197

Sorsby A (1972) Bilateral retinoblastoma A dominantly inherited affection *Brit Med J 2* 580

Tso M O M Fine B S & Zimmerman L E (1970) The nature of retinoblastoma II Photoreceptor differentiation An electron microscopic study *Amer J Ophthal 69* 350

Tarkkanen A & Tuovinen E (1971) Retinoblastoma in Finland 1912—64 *Acta ophthal (Kbh) 49* 293

Tarkkanen, A (1973) Occurrence of mental retardation in patients with retinoblastoma *Acta ophthal (Kbh) 1* 67

Warburg M (1973) Retinoblastoma In *International Ophthalmology Clinics* vol 13 *Genetic Aspects of Ophthalmology* Ed Morton F Goldberg (in press)

Wilson M G Towner J W & Fujimoto A (1973) Retinoblastoma and D chromosome deletions *Amer J Hum Gen 25* 57

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University Eye Clinic (Head Bjorn Tengroth M D)
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TREATMENT OF RETINOBLASTOMA

BY

TORD JERNDAL and BJÖRN TENGROTH

Of the conservative therapeutic methods for retinoblastoma radio therapy is the most efficient The use of Tengroth s ^{60}Co applicator in 20 cases produced a cure in 18 eyes and useful vision was often preserved These results suggest that locally applied ^{60}Co should be used more often

Key words Retinoblastoma — radiotherapy — ^{60}Co applicator — — visual acuity

Retinoblastoma may be treated by radical or conservative measures The choice of method for the individual case depends on the size and location of the tumour The radical methods comprise enucleation of the eye and exenteration of the orbital contents Enucleation is usually chosen if the tumour is classified as stage V according to Reese (1963) or if the tumour threatens to perforate the bulb Exenteration may be resorted to if the neoplasm has invaded the optic nerve head or perforated the ocular coats but in these cases the prognosis for life is very poor

There are many conservative therapeutic methods but radiotherapy is undoubtedly the most efficient (Stallard 1968) Good radiotherapeutic results were also found in the Swedish retinoblastoma series described by Jerndal Lindstedt Svensson and Åkerskog (1973) 69 eyes were treated

with a variety of conservative procedures viz scleral diathermia photocoagulation cytostatics external radiation and local application of ^{60}Co Every successfully treated case had received radiotherapy 12 cases had been treated by ^{60}Co and 10 of these eyes were cured This favourable result stimulated us to re examine all cases treated by ^{60}Co in Goteborg and the results are presented in the present paper

Method

For a description of the ^{60}Co applicator see Tengroth and Rosengren (1969)

Case series

The present series consists of 20 eyes with retinoblastoma in different stages according to Reese s classification (Reese 1963) 15 eyes received primary ^{60}Co-application The remaining 5 eyes received ^{60}Co after unsuccessful attempts with photocoagulation external radiation or cytostatic drugs The follow up periods vary between one and nine years with a mean of four and a half years

The classification of the tumours at the time of diagnosis and the cure rate are shown in Table I

18 eyes classified in groups I—IV were cured, but one eye developed a late recurrence after 6 years Only 2 eyes were lost to enucleation, but these two were advanced cases and classified as IV and V

The doses of radiation are expressed in rads at 2 mm distance from the sur face of the spherical applicator and are calculated for each case (Table II)

It is encouraging to find that 5 eyes were cured by one single application 2 of which were classified as III The necessity for repeated applications of ^{60}Co

Table I
Therapeutic results of ^{60}Co (20 eyes)

Classification Reese		I	II	III	IV	V
Cured	primary ^{60}Co	4		6	2	1
	secondary ^{60}Co			2	2	
Not cured	primary ^{60}Co					1
	secondary ^{60}Co				1	
Late recurrence					1 (6 years)	

Table II

Calculated doses with ^{60}Co (20 eyes)

	Name	Number of applications	Dose rad	Period of observation years	Complication
Group I	J P	1	4 680	4	
	S H	3	5 690 × 3	3	
	B L	1	5 910	1	
	S N	1	5 830	1	
II	—				
III	H A	2*	5 580 × 2	6	cat
	E J	1	6 090	5	
	J S	2	5 103 + 3 274	9	
	L O S	3	3 400 × 3	8	
	S T	2	4 900 × 2	8	
	C Ö	2	4 930 × 2	4	
	L A	1	5 605	6	
	A S	2*	10 960 + 3 380	1	
IV	H K	9	4 700 × 9	3	cat + phthisis
	A O	2	2 140 + 1 330	9	cat
	C B	5	5 580 × 5	5	cat
	D S	5	4 200 × 5	3	not cured
	U P N	7	6 300 × 7	6	cat
	S J	3	4 530 × 3	1 5	cat
V	T N	4	5 700 × 4	6	cat + phthisis
	F E	3	3 000 + 2 × 1 570	1	not cured

* also external radiation

Table III

Visual results after ^{60}Co (20 eyes)

Group	I	II	III	IV	V
≥5/5	1		4		
5/10—5/5					
5/50—5/10			3	1	
1/60—5/50				2	
P —1/60					1
O				2	1
cured vision not tested	3		1	1	

for new tumours or recurrences increases the risk for irradiational complications such as cataract and phthisi On the other hand Table II shows that 2 eyes received three applications each without any complication.

The visual results are given in Table III A particularly interesting result concerns the 8 cases in group III which according to Reese have a doubtful prognosis Not only were these 8 eyes cured but they also retain useful vision — 4 of them even 5/5 or more

Conclusion

The result of the ^{60}Co-therapy with Tengroth s applicator has made us change our therapeutic attitude towards retinoblastoma Thus we never treat cases classified as I—IV by primary enucleation but attempt local application with ^{60}Co If an adequate dose is given the tumour will rapidly shrink and a co-existing retinal detachment will diminish or disappear within 3—4 weeks This therapeutic response is truly dramatic and an apparently »lost» eye may be saved and some vision preserved

The posttherapeutic follow up must be scrupulous and continue first once a month then once every second month for about two years If new tumours appear they are promptly treated by re-application of ^{60}Co and are easily eradicated if they are small

In one special situation early discovery of the primary tumour is possible namely in families with inherited retinoblastoma The prognosis for such early cases usually classified as I—III is extremely favourable with adequate local application of ^{60}Co

References

Jerndal T Lindstedt E Svensson T & Akerskog G (1973) Retinoblastoma in Sweden *Acta ophthal (Kbh) 51* 543

Reese A B (1963) *Tumours of the eye* Harper and Row New York

Stallard H B (1968) The treatment of retinoblastoma *Bibl ophthal (Basel)* ~ 149

Tengroth B (1962) En modifikation av Stallards koboltapplikator vid behandling av retinoblastom. *Nord Med 68* 1400

Tengroth B & Rosengren B H O (1969) The treatment of retinoblastoma with a ^{60}Co application *Acta ophthal (Kbh) 47* 44

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Eye Pathology Institute (Head S Ry Andersen) Anatomy Department B (Head E Landboe Christensen) and the University Eye Department (Heads J Edmund and E Gregersen) University of Copenhagen Copenhagen Denmark

EFFECT ON GROWTH AND STRUCTURE OF TRANSPLANTABLE MALIGNANT MELANOMAS OF THE SYRIAN GOLDEN HAMSTER *(MESOCRICETUS AURATUS)* BY DEPLETION OF PHENYLALANINE AND TYROSINE IN THE DIET AND BY INHIBITION OF TYROSINASE

Brief report

BY

O A JENSEN J EGEBERG and J EDMUND

(The full report has been published in Acta path microbiol scand section A *81* 559—568 1973)

Probably tumour cells cannot withstand deficiencies of certain nutrients for as long as normal cells The neoplastic cell may have specific requirements for nutrients that make it highly vulnerable to dietary or biochemical deficiencies The melanoma cell is an example of such a cell (Bertino & Nixon 1969)

Since we had observed promising effects from a low phenylalanine-tyrosine diet in a patient with a primary choroidal malignant melanoma (see J Edmund O A Jensen & J Egeberg this issue) the present work aimed experimentally to study the same diet s effect on the melanoma cell particularly the light microscopical and ultrastructural changes

Material and methods

The diet consisted of a phenylalanine tyrosine free powder Tyrogran supplied by Nyegaard & Co A/S Oslo Norway The composition of this powder is given in Table I Copper an activator of tyrosinase was chelated by D penicillamine and precipitated by Na_2S Since phenylalanine and tyrosine are amino acids essential to life the necessary minimum of these acids was secured by giving small amounts of turnip which has a low content of these amino acids Control animals were fed a normal hamster chow

Two experiments were carried out Each experiment used about 50 animals half of which were controls Tumours were induced by injection of homogenized tumour tissue subcutaneously In the first experiment the diet was instituted after transplantation of the tumour In the second tumour transplantation was carried out after institution of the diet The experiments continued until all animals had died when they were examined at necropsy and the number of metastases counted Tumour tissue from all dead animals was examined light microscopically and tissue from some of them was examined ultrastructurally Normal animals kept on the diet for over a year and a half were also examined particular attention being paid to the skin and genital organs

Results

In the first experiment no difference in survival period between the controls and the animals fed the diet was found In the second experi

Table I
Amino acid analysis of diet powder

	mmol/g
Glutamine + Glutamic acid	0 65
Proline	0 40
Lysine	0 25
Leucine	0 24
Asparagine + Aspartic acid	0 19
Valine	0 19
Serine	0 18
Alanine	0 15
Glycine	0 11
Threonine	0 11
Isoleucine	0 11
Arginine	0 076
Histidine	0 055
Phenylalanine	0 0
Tyrosine	0 0

Methionine Cysteine + Cystine and Tryptophan are destroyed by the method of analysis

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(The full report has been published in Acta path microbiol scand section A 81 559—568 1973)

Probably tumour cells cannot withstand deficiencies of certain nutrients for as long as normal cells The neoplastic cell may have specific requirements for nutrients that make it highly vulnerable to dietary or biochemical deficiencies The melanoma cell is an example of such a cell (Bertino & Nixon 1969)

Since we had observed promising effects from a low phenylalanine tyrosine diet in a patient with a primary choroidal malignant melanoma (see J Edmund O A Jensen & J Egeberg this issue) the present work aimed experimentally to study the same diet s effect on the melanoma cell particularly the light microscopical and ultrastructural changes

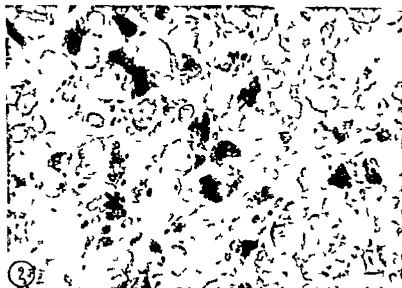


Fig 2

Tumour tissue from diet treated animal Pigment is seen only in melanophages 1 micron section of tumour tissue embedded in epon and stained with toluidine blue (x 550)

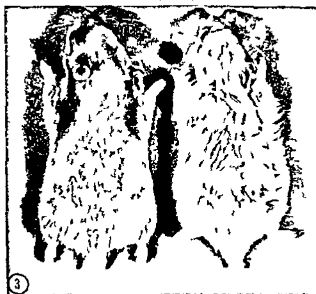


Fig 3

Normally fed hamster (left) compared with a hamster fed the diet for 18 months The diet fed animals develop a grey fur with a somewhat wispy appearance Note the same size and condition of the two animals

Discussion

The rationale of the present dietary treatment for malignant melanoma is the fact that tyrosine (into which phenylalanine can be transformed in the liver) is the basic amino acid in melanin production and that tyrosinase (the basic enzyme in this process) is vital to the metabolism of the melanoma cell (Demopoulos 1962 Demopoulos & Kaley 1963, Demopoulos Gerving & Bagdoyan 1965) Thus depriving the enzyme of its activator and substrate, an inhibiting effect on cell metabolism and thereby on tumour growth might be expected

This dietary treatment had previously been instituted in patients with metastatic malignant melanoma of the skin (Demopoulos 1966) but never, to the best of our knowledge, in cases of primary malignant melanomas and particularly not in ocular melanomas (Edmund Jensen Egeberg to be published)

Our experimental study of the diet s effect shows changes in the structure and substructure of the neoplastic melanocytes and of the skin of normal hamsters exposed to the diet We interpret these changes as an effect on melanogenesis and on the growth of the transplantable malignant melanoma of the Syrian golden hamster Nevertheless the diet cannot prevent the origin or development of this transplantable tumour

In any event we find the results theoretically interesting and this approach by depriving a tumour of specific amino-acids and inhibiting a specific enzyme may be the foundation of a biochemical and dietary method for controlling this fatal tumour in man

Acknowledgements

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References

Bertino J R & Nixon P F (1969) Nutritional factors in the design of more selective antitumor agents *Cancer Res* 29 2417—2421

Demopoulos H (1962) Selective inhibition of S 91 mouse melanoma by phenyl lactate in vitro *Bull N Y Acad Med* 38 509—510

Demopoulo H B (1966) Effects of reducing the phenylalanine-tyrosine intake of patients with advanced malignant melanoma *Cancer* 19 657—664

Demopoulos H & Kaley G (1963) Selective inhibition of respiration of pigmented S 91 mouse melanomas by phenyl lactate and the possibly related effects on growth. *J nat Cancer Inst 30* 611—633

Demopoulos H B Gerving M A & Bagdoyan, H (1965) Selective inhibition of growth and respiration of melanomas by tyrosinase inhibitors *J nat Cancer Inst 35* 823—827

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Discussion

N Ehlers The amino acids tyrosine and phenylalanine are concentrated in human aqueous humour Assuming also a concentration mechanism in the melanoma cell one might wonder whether the tyrosina e inhibition or the avoidance of phenylalanine and tyrosine has the major effect

Answer From our present experiments we cannot decide which of the two factors have the major effect

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Department of Ophthalmology (Head Professor Salme Vannas M D)
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NEURILEMMOMA OF THE CHOROID IN RECKLINGHAUSEN S DISEASE

BY

SALME VANNAS CHRISTINA RAITTA and A TARKKANEN

A rare case of choroidal neurilemmoma in Recklinghausen s disease is reported A 16-yr old schoolgirl had bilateral acoustic cauda equina and choroidal neurilemmoma as well as café au lait patches of the skin The fluorescein angiographic pattern is presented and correlated with the histological findings

Key words Recklinghausen s disease — neurilemmoma (Schwanno ma) of choroid — fluoresceinangiography of neurilemmoma

Recklinghausen s disease is a well-delineated inherited syndrome in which the peripheral nerves central nervous system and the skin are all affec ted The symptomatology and course of the disease vary considerably but it is essentially characterized by multiple hamartomas in different parts of the body Tumours occur most often in the perineural structures of the peripheral nerves and the central nervous system

Neurofibroma involving the uveal tract leading to glaucoma and buphthalmos and often accompanied by neurofibromatoses of the lids and facial skin seems to be the most common variant of the disease (Walsh &

Hoyt 1969) A connection between Recklinghausen s disease and malignant melanoma of the choroid has been reported (Nordman & Brini 1970) Cernea & Dobrescu 1973) Neurilemmoma (Schwannoma) is a rare intraocular manifestation and has been reported by François (1947) This tumour is easily misdiagnosed as malignant melanoma

A case of Recklinghausen s disease with multiple neurilemmomas viz of the acoustic nerves the choroid and the spinal cord is presented with special reference to the fluorescein angiographic pattern To the best of our knowledge the use of fluorescein angiography in histologically verified neurilemmoma of the choroid has not been reported

Case report

Clinical history The patient a schoolgirl aged 12 yrs had a history of impaired hearing Skull X ray showed a bilaterally enlarged acoustic porus The otologist referred the patient for evaluation to the neurosurgical unit where Recklinghausen s disease was diagno ed The girl had also typical cafe au lait patches on the stomach On neuro ophthalmological examination she was found to have normal visual acuity in her right eye nasally a greyish low patch was present and diagnosed as a choroidal tumor Her left amblyopic eye was 6 D myopic exotropic and showed tilting of the disc No signs of papilloedema were present

A tumour weighing 40 gms was removed at craniotomy Histologically it was a neurilemmoma of the so-called type A

After the operation the patient was quite well until she developed headache and increasing ataxia Pneumoencephalography showed the left acoustic tumour had increased in size and was now dislocating the aqueduct of Sylvius Increased intracerebral pressure was present

On preoperative neuro ophthalmologic examination the tumour in the right eye had also increased in size

The differential diagnosis lay between melanoma or neurinnoma of the choroid both of which are known to occur in Recklinghausen s disease The fluorescein angiogram (Fig 1) identified the tumour as arising from the choroid The retinal vessels on the peak of the tumour were dilated it did not contain pigment but there were areas of early underfilling on the peak which easily could be mi taken for pigment In the late phase 25 after the injection the entire tumour showed intense fluorescence The angiographic pattern was interpreted as a heavily vascularised tumour containing little or no pigment

The fluorescein pattern was not comparable with those of melanomas diag nosed earlier in our laboratory and we therefore concluded that we had to deal with a neurinnoma arising from the ciliary nerves No radical therapy was suggested. The girl was taken to the neurosurgical unit for operation on the right acoustic nerve Nevertheless she died a few days later from postoperative com plications

At autopsy a further tumour of the cauda equina was found All specimens were sent for histological examination

Ocular pathology Macroscopically the right eye measured 23 mm in diameter

Microscopically the anterior parts of the eye were apparently normal A solid tumour was found in the choroid It was composed of small spindle cells arranged in twisted bands and accompanied by delicate connective tissue (Fig 3) with no evidence of degeneration Numerous large blood vessels were surrounded by thick collagen sheaths There was no infiltration of Bruch s membrane The retina at the tumour showed some degenerative changes The optic nerve and the posterior ciliary nerves appeared normal Reticulin stain showed a fine net work of argentophilic fibres within the tumour (Fig 4)

Histologically the tumour did not contain pigment but it was richly vascu larized The ves els were lined with collagenous material and a network of reticulin penetrated the tumour The vessels of the tumour were more numerous towards the base a fact that correlated well with the angiographic finding Early underfilling of the pe k w s found to be present

The acoustic nerve tumour was identical with the choroidal tumor (Fig 5)



Fig 3

Choroidal neurilemmoma A distinct palisading pattern is seen with large vascular channels close to the pigment epithelium (arrow) The retina shows degenerative changes C = choroid R = retina V = vitreous Hematoxylin and eosin

Comment

Neurilemmoma is a typical tumour of Recklinghausen s disease and occurs usually in the acoustic nerves and spinal cord Neurilemmoma of the choroid is very rare one case being described by François (1947) who reviewed the literature Up to that date about 5 cases had been reported The typical Schwannoma or neurilemmoma of the choroid is an unpig mented richly vascularized benign tumor During foetal development the axons are encircled by the Schwann cells and during further development there form many turns around the axon This result in the axon s becoming surrounded by multilayered myelin sheath



Fig 4

Choroidal neurilemmoma Reticulin stain reveals a network of delicate argento philic fibres within the tumour Nassar stain

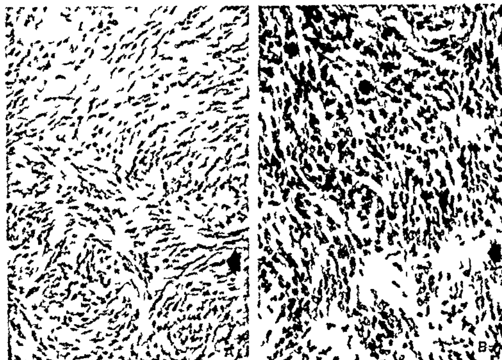


Fig 5
Comparison of the acoustic nerve (A left) and choroidal (B right) tumors The cellular tumours show palisading structures (arrows) Hematoxylin and eosin

Neurofibromatosis is a congenital aberration in which the Schwann cells continue to proliferate The tumours called neurilemmomas, neuri fibromas neurinomas or Schwannomas may therefore arise in any area of the nervous system

Fluorescein angiography is a useful method in differential diagnosis The rich vascularisation of the tumour and hence the very even extensive late fluorescence seem to be the most diagnostic features

Benign and malignant melanomata of the uvea may coexist with cutaneous manifestations of neurofibromatosis (Nordman & Brini 1970 Cernea & Dobrescu 1973) and also with acoustic neurofibroma (Blair Love 1937) To our knowledge however only one case of choroidal neurofibroma and acoustic neurinoma has been described (Moorhause 1939) Our case illustrates the value of fluorescein-angiography in the diagnosis of the rare choroidal neurilemmoma

References

Blair H L & Love G (1937) *Acoustic neurofibroma* associated with melano-epithelioma of the choroid *Proc Mayo Clin 12* 481

Cernea P & Dobrescu G (1973) Melanome malin uvéal manifestation de la maladie de Recklinghausen *Ophthalmologica 166* 161—171

François J (1947) Schwannome intraoculaire *Ann d Ocul 180* 542—546

Gartner S (1940) Malignant melanoma of the choroid and von Recklinghausen s disease *Amer J Ophthal 23* 73

Nordman J & Brini A (1970) Von Recklinghausen s disease and melanoma of the uvea *Brit J Ophthal 54* 641

Walsh F B & Hoyt W F (1969) Clinical *Neuro Ophthalmology* Vol III p 1939 3rd ed The Williams & Wilkins Co Baltimore

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SIMULTANEOUS BILATERAL FLUORESCEIN ANGIOGRAPHY OF THE ANTERIOR EYE

BY

J HELVE and H NIEMINEN

The photographic apparatus used in this study consisted of a Zeiss biomicroscope in which two motor-driven Nikon cameras were connected with one another By using prisms both eyes were photographed simultaneously Photographs were taken at 0 8 sec intervals

In normal persons under 35 years of age the flow always began simultaneously in both eyes In normal people over 60 there were often small time differences in the beginning of the flow Sectoral filling defects were also common in the older age group Brown irises (A Vannas 1969) seldom produced major difficulties in carrying on this test

Simultaneous bilateral retinal angiography (Hisatomi et al 1972) seems to give more exact results in studying carotid occlusive disease with fluorescein angiography Even so studies of several patients with roentgenologically diagnosed carotid occlusive disease with simultaneous bilateral anterior eye fluorescein angiography showed consistently delayed arm-to-retina time on the affected side and often sectoral filling defects of the iris (Karjalainen 1971)

Simultaneous bilateral anterior eye fluorescein angiography may sometimes give additional information in disorders such as glaucoma iritis temporal arteritis and cases where compression of the ophthalmic artery is suspected

References

Karjalainen K. (1971) Occlusion of the central retinal artery and retinal branch arterioles *Acta ophthal (Kbh)* Suppl *109*

Hisatomi C & Suzuki Y (1972) Simultaneous bilateral angiography *Folia Ophthal Jap 23* 239—243

Vannas A (1969) Fluorescein angiography of the vessels of the iris in pseudo exfoliation of the lens capsule capsular glaucoma and some other forms of glaucoma *Acta ophthal (Kbh)* Suppl *105*

Discussion

A Vannas In my thesis in 1969 (Acta Ophthal Suppl 105 1969) I studied patients with an acute attack of angle-closure glaucoma In iris angiography after an attack when tension had been normalised the circulatory dynamics were not normal Profuse fluorescein leakage was noticed from the iris vessels in these patients Later control angiographies showed obliteration of some vessels and development of atrophic areas in the iris

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ULTRASONIC DIAGNOSIS IN MELANOMA AND RETINOBLASTOMA

BY

ARVO OKSALA

The echograms of a melanoma a retinoblastoma and coagulated blood which extends to the posterior wall of the eye are similar but they can easily be distinguished from the echograms of central vitreous haemorrhage vitreous exudation and idiopathic detachment of the retina If the posterior part of the vitreous is normal in retrolental fibroplasia this disease can be distinguished ultrasonically from a retinoblastoma When optic examination is not possible an intraocular tumour which is at least 2 mm in diameter can often be diagnosed and localized with ultrasound

Key words Ultrasound — echogram — melanoma — retinoblastoma

As intraocular melanomas and many cases of retinoblastoma are treated radically i e by enucleation we should strive to achieve the greatest possible certainty in clinical diagnosis Hence a series of cases have been examined by all those methods that increase the reliability of diagnosis Ultrasonic examination is one of the methods which have come into extensive use during the last 15 years

Equipment and method

Several A scan and B-scan apparatuses suitable for ultrasonic examination, manufactured by various companies, are available to ophthalmo-

logists The frequencies used for the ultrasonic examination of the eye are 6 20 MHz considerably higher than in other fields of medicine At an A scan examination the transducer is pressed against the surface of the eye while in a B scan one the production of an acoustic cross section requires free movement of the transducer so that there has to be a column of liquid between the sound head and the eye The diagnostic reliability of both methods for eye examinations is virtually equally good provided the investigator masters the method and the equipment is good For clinical purposes the A-scan has been in continuous use for longer than the B scan because the former is simpler for both patient and doctor A-scan equipment is also much less expensive than B-scan equipment For some 18 years I have always used the A-scan for the examination of melanomas and retinoblastomas B scan has been used when an optic examination has not been possible and more accurate information on the position of the tumour and its relation to the surrounding tissues has been needed

Patients studied

During the last 15 years I have examined by ultrasound 72 choroidal melanomas and 17 retinoblastomas In all cases the diagnosis was verified by histological examination The diameter of the melanomas varied between 2 and 10 mm Among these cases there were 7 eyes with absolute glaucoma in which ultrasonic examination was the only method giving results indicating a melanoma Moreover for these eyes ultrasound gave not a single wrong result In three cases of retinoblastoma the symptoms greatly resembled those of chronic uveitis and an optic examination was impossible

Echograms

Echograms can indicate whether a particular intraocular pathological area contains acoustically homogeneous liquid (such as subretinal fluid) or acoustically slightly nonhomogeneous liquid (such as exudation) or acoustically quite heterogeneous solid tissue (such as a melanoma or a retinoblastoma) In all the above-mentioned cases of tumours the echograms indicated pathological solid tissue inside the eye The clinical diagnosis of most of these cases was naturally based on the results of several methods of examination above all optical ones As the echograms

of melanomas and retinoblastomas are often quite similar I will present here A-echograms and B-echograms of one melanoma and one retinob lastoma

Fig 1 A represents an A-echogram of a choroidal melanoma and Fig 1 B the corresponding B-echogram The tumour was oval and the A-ech ogram was obtained when the sound beam travelled via the longest diameter of the tumour On the left in Fig 1 A one sees the initial impulse the arrow in the middle points at echoes reflected by the surface of the tumour and the arrow on the right indicates the echoes reflected by the rear wall of the eye The melanoma is clearly acoustically heterogeneous throughout the whole direction of examination even if its rear part reflects only low echoes These low echoes are due to the fact that the maximal intensity of the sound waves was not used at the exami nation and this may also be seen in the shape of the highest echopeaks Typically in the echogram of a melanoma the tumour reflects a continuous group of fairly high echoes all the way to the rear wall echoes

The B-echogram in Fig 1 B was obtained at the maximal intensity The surface of the tumour appears quite distinct but its interior reveals acoustically homogeneous areas which have also been called acoustic vacuoles At B-scan examination the movement of the transducer was linear and this method produces larger acoustically homogeneous areas than would occur with so called compound scanning

Fig 2 A represents an A-echogram of a retinoblastoma and Fig 2 B the corresponding B-echogram On the left in Fig 2 A one can see again the initial impulse The arrow in the middle indicates the echoes reflected by the surface of the retinoblastoma and the arrow on the right points to the echoes reflected by the rear wall of the eye The echoes from the retinoblastoma are here fairly high even if the maximal intensity was not used at the examination At an A-scan examination a retinoblastoma resembles a melanoma in that it often reflects a continuous group of fairly high echoes extending all the way to the echoes arising from the rear wall of the eye If the retinoblastoma contains a necrotic area with a diameter of some millimetres only low echoes can be obtained from it even if the intensity used is quite high Fig 2 B represents the B echogram of a large retinoblastoma The echogram is very similar to that of the melanoma described above The surface of the tumour is clearly visible but the interior contains acoustically homogeneous areas At this examination the movement of the transducer was also linear

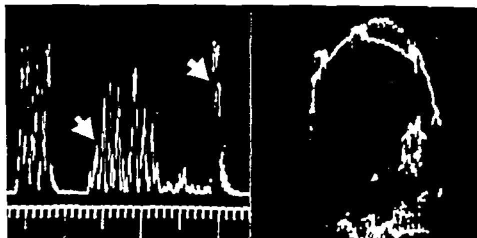


Fig 1 A
An A echogram of a choroidal melanoma

Fig 1 B
The corresponding B echogram

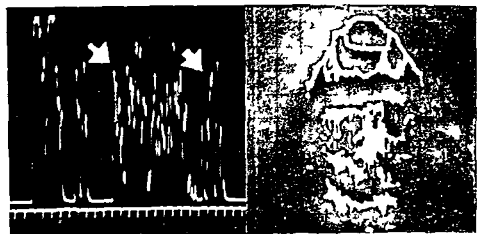


Fig   A
A echogram of a retinoblastoma

Fig 2 B
The corresponding B echogram

With the ultrasonic equipments I have been using the A-scan has been distinctly more sensitive and reliable than the B-scan in the diagnosis of both melanoma and retinoblastoma The finding of solid tissue is possible only with A-scan

Differential diagnosis

With present equipment the capacity of ultrasonic examination is not sufficient to differentiate between the various tumours such as melanomas retinoblastomas haemangiomas and various metastatic tumors Nor can one use echograms to distinguish coagulated blood which extends to the rear wall of the eye from tumours One can, however differentiate between tumours and quite extensive haemorrhage if the haemorrhage is in the middle of the vitreous and is separated from the rear wall of the eye by undamaged vitreous Fig 3 represents the echogram of an extensive haemorrhage in the middle of the vitreous and there is a distinct zero line between the haemorrhage and the fundus In cases such as this the pathological area naturally has to be examined from several different directions

An intraocular tumour protruding from the rear wall of the eye may be discovered and localized by ultrasound if its height is at least 1 5 mm

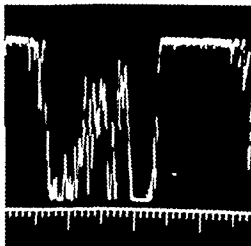


Fig 3
An echogram of an extensive haemorrhage in the middle of the vitreous

Differential diagnosis by ultrasound is possible only if the tumour is at least 2 mm high An idiopathic detachment of the retina is easily discernible by ultrasound alone A detached retina emits a high and narrow echo from a large area in the fundus and the subretinal fluid is acoustically homogeneous In an exudative detachment of the retina the subretinal space reflects distinctly lower echoes than a tumour If the posterior part of the vitreous is normal in a case of retrolental fibroplasia, this condition can be distinguished from a retinoblastoma by ultrasound As the vitreous exudation which occurs in chronic uveitis reflects echoes clearly lower than those of a retinoblastoma and, as the echoes of an exudation also differs from them in being mobile it is usually possible ultrasonically to distinguish a retinoblastoma from chronic uveitis

Discussion

L Ericson The possibilities to differentiate between malign melanoma and subchoroidal bleeding?

Answer You cannot with echograms alone differentiate between a melanoma and organized blood If for example suprachoroidal haemorrhage contains areas with a diameter of at least 2—3 mm which has moving red corpuscles this movement can be seen in the echogram.

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CHEMOTHERAPY IN INTRAOCULAR METASTASIS FROM CARCINOMA OF THE BREAST

BY

HENRY AASVED and VIDAR SEIM

Carcinoma of the breast is often the primary le ion when intraocular metastases occur Usually these patients will also have metastases elsewhere In addition to hormonal therapy it seems logical to regard nonhormonal chemotherapy as the treatment of choice Two ca es with uveal metastases from breast cancer are presented

Key words carcinoma of the breast — intraocular metastasis — chemotherapy

Intraocular metastases are much more infrequent than primary tumours of the eye The actual frequency of metastases in this organ is uncertain owing to the following factors they often occur terminally they may not produce symptoms histopathological examination of the eyeball is not a routine procedure at autopsy when a neoplasm has been diagno ed else where

Most metastases occur in the posterior portion of the uvea and are bilateral in 20—25 per cent of cases The breast and lungs are by far the most common site of the primary lesion thereafter in decreasing order of frequency they may arise in the skin genitals, kidney and gastrointestinal tract (Godtfredsen 1944 Greear 1950 Reese 1963 Albert et al 1967 Jensen 1970 1969 Bloch and Gartner 1971)

Metastases from the lungs usually occur within one year of diagnosis of the primary tumour By contrast very few cases of breast carcinoma metastasize to the eye in less than 1—2 years (Jensen 1970 1969)

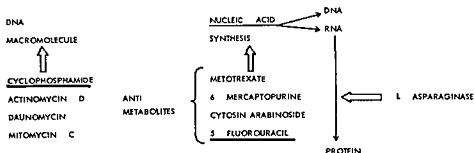
Therapy

Intraocular metastases from carcinoma of the breast usually indicate a progressive disease with metastases elsewhere and hence systemic treatment will often be necessary Regression of intraocular metastases has been observed on hormone therapy alone or in combination with *oophorectomy or other ablative endocrine surgery* Positive results with local x-ray treatment have also been reported (Cordes 1944 Dickson 1958 Reese 1963) Enucleation is indicated only when intractable secondary glaucoma has developed

The use of cytostatic drugs in the treatment of these patients has increased during the last 10 years Fig 1 shows the most commonly applied cytostatics and their essential site of action Most of these drugs act by attacking the macromolecular DNA or by interfering with DNA-synthesis This cyclophosphamide is an alkylating agent which attacks macromolecular DNA 5-Fluorouracil is an antimetabolic agent which disturbs DNA synthesis

Fig 2 shows the cell cycle which is largely the same in normal and malignant cells For different cell types the phases S (DNA-synthesis) G 2 (production of RNA and protein) and D (dividing phase mitosis) have relatively much the same duration G-1 is the phase of the cell cycle with the greatest variation in length The proliferation rate will therefore depend on the duration of G 1 Consequently a short G-1 means rapidly dividing cells and vice versa G 1 is also the phase of the cell cycle in which those cells which are not dividing are more or less »resting cells

With a short G-1 the S phase will be the best point of attack Hence it will be of value to use an inhibitor of DNA-synthesis for example 5-Fluorouracil a relatively cycle specific agent



Bloch R S & Gartner S (1971) The incidence of ocular metastatic carcinoma *Arch Ophthal 85* 637

Carter S K. (1972) Single and combination nonhormonal chemotherapy in breast cancer *Cancer 30* 1543—1555

Cline M J (1971) Cancer chemotherapy In *Major problems in internal medicine* vol I W B Saunders Philadelphia London Toronto

Cordes F C (1944) Bilateral metastatic carcinoma of the choroid with x ray therapy to the eye *Amer J Ophthal 27* 1355—1370

Costanzi J J & Coltman C A Jr (1969) Combination chemotherapy using Cyclophosphamide Vincristine Methotrexate and 5 Fluorouracil in solid tumors *Cancer 23* 589—595

Dickson, R J (1958) Choroidal metastasis from carcinoma of the breast *Amer J Ophthal 46* 14—18

Godtfredsen, E (1944) On the frequency of secondary carcinomas in the choroid *Acta ophthal (Kbh) 22* 394—400

Greear J N Jr (1950) Metastatic carcinoma of the eye *Amer J Ophthal 33* 1015—1025

Greenwald E S (1973) *Cancer chemotherapy* 2nd ed Hans Huber Publishers Bern Stuttgart Vienna

Jensen O A. (1969) Metastatic tumors of the eye and orbit *Acta Path microbiol scand* Suppl *212* 201

Nemoto N & Dao T L. (1971) 5 Fluoruracil and Cyclophosphamide in disseminated breast cancer *N Y State J Med 71* 554—558

Price L. A & Goldie J H (1971) Multiple drug therapy for disseminated malignant tumours *Brit Med J 4* 336—339

Reese A B (1963) *Tumors of the eye* 2nd ed p 514—528 Hoeber Medical Div N Y Evanston London

Discussion

E Vesterdal A case material of 14 consecutive choroidal metastases in females with breast cancer treated in the Finsen Institute Copenhagen 1966—1970 is reported They are all dead now Treatment all patients received glucocorticoids in the high dosage In addition 7 preclimacterial women had ovarial x-ray treatment and 5 androgen hormones Duration of treatment (from time of diagnosis till death) 3—26 months Average 11 months Visual acuity was measured in all patients a few days before death Results 12 patients had 6/6 in at least one eye One had 6/12 (senile macular degeneration) and only one had 6/36 (because of too late ovarial x-ray treatment) Conclusion Owing to too late diagnose the prognosis of the first attacked eye in some cases was bad but vision of the second eye was saved in all patients until time of death Cytostatic treatment has not been necessary

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RADIATION TREATMENT OF INTRAOCULAR CANCER METASTASES

BY

E NORDMAN and L. E O NORDMAN

Three cases of breast cancer with intraocular metastases treated with radiotherapy are presented. In three eyes out of four scar formation of the metastases could be observed Remarkable improvement of vision was noticed in two eyes No cataract could be observed even after a survival time of over 3 years owing presumably to the direction of the radiation beam behind the lens Because even patients with metastatic breast cancer may live for a relatively long time palliative radiotherapy can be recommended for eye metastases

Key words ocular metastases — breast cancer — radiotherapy

Improved methods of treatment of metastatic cancer have led to an increased frequency of patients with intraocular metastases According to Orenstein *et al* (1972) only about 500 cases have been described In Godtfredsen s study (1944) only 6 out of 8700 cancer patients had metastases in the eye Albert *et al* (1967) in a 2 year follow-up study of 213 patients with metastases in other parts of the body found eye metastases in 2 % In autopsies of 1000 patients with malignant tumours Guthert *et al* (1965) found only 5 cases with intraocular metastases In their

series however the cancer had spread farther than the regional lymph nodes in only 594 of the cases so that eye metastases occurred in about 1 %

Breast cancer is the form of cancer that most often produces metastases in the eye presumably because of its relatively slow course Thus whereas the 5 year survival rate of lung cancer is 5 % that of breast cancer is 50 % From 60 to 70 % of all clinically verified metastases in the eye have their origin in breast cancer Albert *et al* stated that eye metastases were found in 8 % of 52 cases of metastatic breast cancer Of 31 cases of chorioidal metastases treated with radiotherapy Haye and Calle (1972) found that only 5 did not originate in the breast

Material and methods

Three patients are presented with eye metastases treated with radiotherapy (Table I) These patients had breast cancer with skeletal metastases and one also had lung metastases These metastases had been verified either simultaneously with or before the occurrence of the eye metastases 1 patient had received hormone and cytostatic treatment 4 months before the appearance of the eye metastasis the others had begun hormone treatment at the same time as eye radiotherapy In all 3 cases the disease continued to disseminate in spite of hormone therapy The eye symptoms consisted of reduced visual acuity or light phenomena In two cases only one eye had become involved in the other case both eyes had metastases 2 of the patients were treated with conventional 200 kV x ray equipment from lateral fields to the diseased eye to exclude the lens from the radiation beam. The tumour dose was about 2800 rads In the third case a dose of 4400 rads was delivered with cobalt 60 to both eyes and in this case also attempts were made to protect the lenses The follow up time was from 11 to 39 months

Table I
Eye metastases in breast cancer patients

	Breast surgery	Metastases other than ocular	Eye metastasis	Latency time after mastectomy
1 H S 44 yrs	VI/67	Lung IV/68 Skeletal IV/69	V/69 o d	23 months
2 G M 74 yrs	X/68	Skeletal VIII/71	VI/71 o s	28 months
3 A H 43 yrs	VIII/68	Skeletal X/68	X/68 o a	2 months

Table II
Radiotherapy of eye metastases.

	Radiotherapy	Immediate results	Subsequent course	Last ocular status
1 H.S 44 yrs	2 800 rads 200 kv	Metastasis diminished V 0 7 → 0 8	Died after 11 mo	Retinal detachment
2. G M 74 yrs	2 800 rads 200 kv	Scar formation V 0 05 → 0 4	Alive after 24 mo	No recurrenc
3 A H 43 yrs	4 400 rads Co-60	Scar formation o a V OD 0 4 → 1 0 OS 1.25 → 1 0	Died after 39 mo	No recurrenc

Results

In case 1 the tumour became smaller and the visual field scotoma wa diminished after x-ray treatment At the terminal stage 11 months afte the treatment the patient had a large retinal detachment in the disease eye (Table II)

At the beginning of x-ray treatment case 2 had a visual acuity of 0 05 The acuity rose to 0 4 after radiation treatment (Fig 1 and 2) The patien is alive after more than 2 years and has no radiation cataract

Case 3 had metastases in both eyes In one eye the visual acuity ros from 0 4 to 1 0 in the other it deteriorated slightly from 1.25 to 1 0 Thi patient lived 39 months after detection of the metastases Despite suc a long survival no cataract could be observed at the last examination 3 months after the cobalt treatments

Discussion

In these patients resolution of the metastases with scar formation occurre in 3 out of 4 eyes treated with radiation therapy Because the radiatio is directed behind the lens no cataract could be observed, and hence i is unnecessary to take into account the possible risk of radiation change of the lens in case of ocular metastasis Untreated patients often develo painful glaucoma necessitating enucleation of the eye Without treatmen case 3 would have been blind for the last three years of her life Th

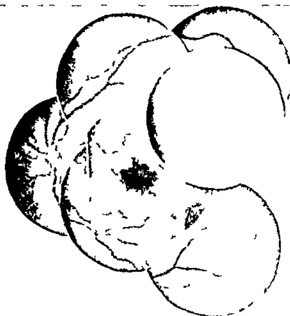


Fig 1

G M 74 year old breast cancer patient (ca e 2) with a choroidal metastasis in the left eye Visual acuity 0 05



Fig 2

Case 2 after treatment with 2800 rads by conventional x ray equipment Scar formation in the area of the metastasis Visual acuity 0 4

survival of these patients is relatively long, i.e. from 11 to 39 months. All lived over 10 months, the average survival time for patients with metastatic breast cancer (Dickson 1958). The longest survival with ocular metastases, 57 months, was reported by Cogan and Kuwabara (1954).

References

Albert, D. M., Robinstein, R. A. & Scheie, H. G. (1967): Tumor metastasis to the eye. I. *Amer. J. Ophtal. 63:* 723—726.

Cogan, D. G. & Kuwabara, T. (1954): Metastatic carcinoma to eye from breast (effect of endocrine therapy). *Arch. Ophtal. 50:* 240—249.

Dickson, R. J. (1958): Choroidal metastases from carcinoma of the breast. *Amer. J. Ophtal. 46:* 14—18.

Godtfredsen, E. (1944): On the frequency of secondary carcinoma in the choroid. *Acta ophthal. (Kbh.) 22:* 394—400.

Guthert, H., Janisch, W. & Possbach, K. (1965): Über die Haufigkeit der Augenmetastasen. *Munch. med. Wschr. 107:* 939—941.

Haye, C. & Calle, R. (1972): Tumeurs metastatiques choroidiennes. *Ann. d'Oculist. 205:* 549—556.

Orenstein, M. M., Anderson, D. P. & Stein, J. J. (1972): Choroid metastasis. *Cancer 29:* 1101—1107.

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Discussion

T. Jerndal: Why do you choose external radiation and not local application?

Answer: We did not use local cobalt[60] because we think that we will get as good results with external radiation.

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13–16 June 1973

Department of Ophthalmology (Head Prof S Vannas)
University of Helsinki Finland

BASAL CELL CARCINOMA OF THE EYELIDS

A clinicopathologic study of 174 patients

BY

A TARKKANEN and L MERENMIES

Will be published in extended form in Acta Ophthalmologica later on

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
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Department of Ophthalmology (Head Professor T I Bertelsen M D)
University of Bergen Norway

CAUSES OF BLINDNESS AND SEVERE VISION IMPAIRMENT IN CHILDREN
A REGIONAL INVESTIGATION

BY

MAGNUS ODLAND

This work is part of a larger project whose purpose was to investigate as thoroughly as possible the incidence and causes of blindness and severe visual impairment in a specific area The area chosen was the city of Bergen and Hordaland County with a population of 374 288 The examination of the persons concerned was performed by the author personally through an extensive field study

The classification of blindness accepted by the International Association for Prevention of Blindness was used in the present study which showed that 130 children between 0 and 19 years had vision of 6/18 or worse (1 04 ‰) A total of 18 children were totally blind (amaurosis) 14 children were practically blind (v a 1/60 amaurosis) 20 socially blind (v a 6/60—1/60) 66 partially sighted (v a 6/18—6/60) and in 12 children the degree of vision could not be classified Among the cases there was an excess of boys 84 boys compared with 46 girls

The commonest cause of impaired vision was congenital cataract followed by optic nerve atrophy excessive myopia nystagmus and albinism In addition several congenital and hereditary diseases had often resulted in profound visual impairment 49 (38 %) had additional handicaps such as mental retardation motor disturbance hearing defects and Down's syndrome

To be published later in Acta Ophthalmologica

crepancy may be due to the University Hospital s having proportionally fewer cases of squint — those most often in need of glasses

Two other facts are worth mentioning In the various districts 49—68 % of the children were sent to an ophthalmologist by Child Advisory Clinics an indication of how effectively these institutions function in Fin land

4 0 to 23 % of the families of these children did not take the advice to bring them for a follow-up examination thus leaving the therapy uncompleted The lowest figure is that found at the Rovaniemi Central Hospital a district where ophthalmologists are the busiest and often the distances from the Central Hospital are long Thus here visits to hospital for observation were suggested less often and only with very good reason Possibly also the patient — maybe with a feeling of insecurity — was compelled to attend for examination when this was suggested in spite of of because of the long distance to the hospital

More generalized results from this investigation in which the ophthalmological pattern of the child population concerned will be correlated with the varying socioeconomic factors relating to the family and its place of residence and also with illnesses other than ophthalmic diseases have yet to be worked out When this investigation is completed we may look forward to obtaining answers to many unsolved questions and to receiving more detailed information about the development of the child population

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13—16 June 1973

Eye Department (Head S E Lorentzen)
Centralsygehuset Esbjerg Denmark and
the Ophthalmic Pathology Laboratory (Head S Ry Andersen)
University of Copenhagen Denmark

DYSKERATOTIC MARGINAL KERATOCONJUNCTIVITIS IN HEREDITARY PERIODONTOPATHY AND HYPERKERATOSIS

BY

J HVIDBERG HANSEN F ERLIN LARSEN and J KLEENER

An otherwise healthy boy exhibited precocious periodontopathy with extrusion of both the deciduous and the permanent teeth and cutaneous hyperkeratosis as well as relap ing keratoconjunctivitis

On histological examination the gingiva dermis and conjunctiva showed parakeratosis in the epithelium. The father of the patient but not other members of the family showed cutaneous and ocular symptoms of same type The classification of the case is discussed especially its relation to the Papillon—Lefevre syndrome

Key words keratitis — conjunctivitis — periodontopathy — cutaneous hyperkeratosis — Papillon — Lefévre syndrom.

The combination of hereditary cutaneous hyperkeratosis and corneal changes has been described (Spanlang 1927 Wychgram 1952) though in only a very few cases The simultaneous occurrence of hyperkeratotic skin lesions of palms and soles and dental abnormalities was described as a syndrome by Papillon & Lefevre in 1924 and has since been reported on about 50 occasions (Corlin *et al* 1964)

In the Ophthalmic Department at Esbjerg we have seen a case of marginal keratopathy of a peculiar appearance which was difficult to treat The patient was a boy who also displayed skin manifestations and exfoliation of the erupting teeth As the boy s conjunctiva presented

a peculiar histological picture and as his father showed similar signs including ocular changes we felt justified in presenting the case history and our diagnostic speculations

Case report 1

The patient a normally developed boy aged 11 years was admitted with a unilateral resistant keratoconjunctivitis Apart from the conditions to be described he was in good health and mentally normal At the age of two years he had been treated repeatedly at the Dental school Århus for pronounced hyperplastic gingivitis of both the upper and the lower gum and both the gingival tissues and the teeth had had to be removed The oral cavity then gave no trouble until the eruption of the permanent teeth which was associated with another attack of hypertrophic gingivitis The latter did not subside until the patient had had all his teeth extracted He now has a full dental prosthesis As early as the age of 3—4 years the boy presented skin lesions manifesting them selves as follicular hyperkeratoses on arms and legs and hyperkeratotic plaques after minor injuries These latter might persist as hyperkeratotic skin reactions for months — or even years but resolved with time leaving cicatrices and pigmentary changes Histological examination of a biopsy specimen of the skin taken from the patient s arm at the age of 4 years showed epithelial hyperplasia hyperkeratosis and nonspecific chronic granulation tissue The skin lesions had varied little in the course of years More particularly no seasonal variations had been noticed The palms and soles had not been subject to hyperkeratosis

The eye lesion also began at the age of 4 years as keratoconjunctivitis of the left eye with vesicular opacity in various limbal regions and several epithelial opacities on the cornea The lesion subsided with treatment with ultracortenol during stay in hospital The patient had no eye complaints until he consulted us at the age of 11 years After a minor injury due to the point of a graphite pencil having just touched his eye a protracted inflammatory state developed with a bank like marginal thickening extending on to the cornea along its whole periphery The conjunctiva was greyish over the area of its limbus in some places succulent and there was blood vessel invasion of the cornea along its whole margin The central corneal areas showed no signs of keratitis and there was no intraocular reaction Sequelae of vascular invasion were seen superiorly on the right side The patient had previously been treated with chloramphenicol iduridine ointment and a steroid preparation by his own ophthalmologist Culture of material from the conjunctiva showed no growth of bacteria or of fungi The ordinary laboratory tests gave normal results Eosinophilic leucocytes were at the upper extreme of the normal range

A biopsy specimen was taken from the conjunctival limbus at 11—12 o clock The patient was treated initially with atropine and chloramphenicol and later terramycin with polymyxin B and pimafucin ointment

The lesions faded over about 6 weeks At follow up 6 and 12 months later no sequelae were noticed beyond regressing almost bloodless vessels in the periphery of the cornea His vision was above 6/9

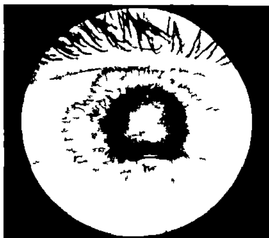


Fig 1
Clinical appearence of the left eye in case 1 at the time of biopsy

Case report 2

The boy s father aged 31 at the time of the examination had had similar lesions of both eyes and skin but allegedly no dental anomalies in relation to the eruption of his teeth Even so he had had to have all his teeth extracted as early as at the age of 16 despite ostensibly careful dental hygiene No data are available from a dentist

Since the age of 5 or 6 he had been troubled by and repeatedly been admitted to hospital with skin lesions of the same nature as those described in the son Biopsy of a skin specimen taken at the Finsen Institute Copenhagen when he was about 16 showed nonspecific subepithelial cell infiltration and a mildy hyperkeratotic squamous epithelium.

In childhood he was repeatedly admitted to an ophthalmic unit with a diagnosis of scrofulous keratoconjunctivitis Nevertheless on retrospective assessment the changes were found not to be typical of scrofulosis but to be compatible with those described in the son s case A recent examination of the father showed impaired vision of the right eye scattered superficial corneal opacities and sequelae of previous blood vessel invasion limbally in both eyes

Predisposition no other family members than the two described here presented a similar picture There was no parental consanguinity

Histopathological examination (case 1)

Histologically a biopsy specimen from the gingiva showed slight hyperplasia and parakeratosis of the epithelium with slight dysplasia of the basaloid layers

Histologically a biopsy specimen from the bulbar conjunctiva showed a similar dyskeratosis with parakeratosis of single epithelial cells (Eye Path. Inst no 194/72)

a peculiar histological picture and as his father showed similar signs including ocular changes, we felt justified in presenting the case history and our diagnostic speculations

Case report 1

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A new syndrome of prenatal-onset growth failure characterized by muscle liver brain and eye involvement and thus named mulibrey nanism was described in 1970 by Perheentupa and coworkers (Perheentupa *et al* 1970) A triangular face with bulging forehead low broad nasal bridge and a mildly hydrocephalic aspect prominent veins on the forehead and neck and thin and hypotonic extremities make up the characteristic appearance of patients with this syndrome while the voice is also peculiar

Very probably this condition is an autosomal recessive and we have now been observed a total of 23 cases and have clinical and autopsy data of a further case The clinical picture has been clearly delineated (Perheentupa *et al* 1973 b c) We wish to call the attention of ophthalmologists *to this syndrome because ocular changes seem to* be a regular feature and while characteristic enough to be helpful in the diagnosis they are yet easily overlooked

Table I

Findings in 24 patients with mulibrey nanism. (12 male 12 female age from 4 months to 14 years)

Birth length ≥ 1 5 SD below mean for gestational age (below 47 cm at term)	19/20
Birth weight ≥ 1.5 SD below mean for gestational age (below 2 7 kg at term)	19/24
Present height ≥ 3 0 SD below mean for age and sex	23/24
Present weight ≥ 1 5 SD below mean for age and sex	14/24
Relative sitting height ≥ 1 5 SD above mean for age and sex	16/23
Triangular face	24/24
Characteristic small voice	24/ 4
Muscle hypotonia	19/24
Hepatomegaly liver edge ≥ 2 cm below costal margin	14/24
Prominent veins on neck	[illegible]1/24
Ascites oedema and/or frank pulmonary congestion	7/24
Definitely enlarged heart	2/24
Prominent left atrium and/or right ventricle	19/24
Abnormal ECG	18/24
Proved pericardial constriction	6 24
Long shallow sella turcica	23/24
Abnormally large cerebral ventricles and cisternas	6/6
Pigment dispension and drusen in ocular fundi	22/23
Hypoplasia of choriocapillaris in fluorescein angiography	11/11
Cutaneous naevi flammei	17/24
Fibrous dysplasia of tibia	[illegible]/23

Clinical course

The pregnancies in the mothers of these children had been uneventful and 20 of the 24 patients were born within 2 weeks of term Most had clearly suffered retardion of growth during intrauterine life (Table I) The birth weights of the series showed a mean of 1 8 and the height 2 2 standard deviations below the means of healthy newborns of the same gestational age These means correspond to a 45 5 cm and 2 6 kg size of an infant born at term Eight of the patients had asphyxia or cyanosis in the immediate postnatal period One had to be digitalized on the third day of life for congestive heart failure, she died at 1 3 years of age with persisting heart failure Six others developed oedema and ascites or features of severe pulmonary congestion at an age which varied from 2 to 20 years and one died at 10 years of age The motor development and later the physical capacity were normal or slightly impaired except for those who had cardiac failure The intelligence was at or slightly below the level of the family The skull was relatively large and in nine cases a pediatrician s suspicion of hydrocephalus was recorded The growth failure was progressive Pubertal development was a few years later than average and four of the postpubertal girls had oligomenorrhoea

General physical findings

The present size of the patients is shown in Fig 1 a and b and the typical appearance of the patients in Fig 2 and 3 The heights ranged from 2 7 to 7 7 (mean 5 0) standard deviations below the mean for age and sex Gracility was a characteristic feature especially in the children The extremities were short for the length of the trunk this feature was conspicious in some cases and statistically valid for the whole series The growth of the facial skeleton was impaired as compared with the skull and the face had a triangular shape with a bulging forehead and a low broad nasal bridge In most prominent veins were visible on the forehead and neck All had a characteristic small voice slightly hoarse and of high pitch Five had moderate or slight dysarthria General muscular hypotonicity was evident especially in the infants and young children

Slight or moderate enlargement of cerebral ventricles and cisternas was found in all the six patients appropriately studied The base of the skull was characteristic in all but one a long J-shaped sella turcica and

FEMALES MALES

HEIGHT HEIGHT

WEIGHT WEIGHT

Fig 1 a and b

Heights skeletal ages and weights of patients with the mulibrey syndrome The heights have been plotted both at chronological age (black dots) and at skeletal age (circles) and where apart these have been connected with a line

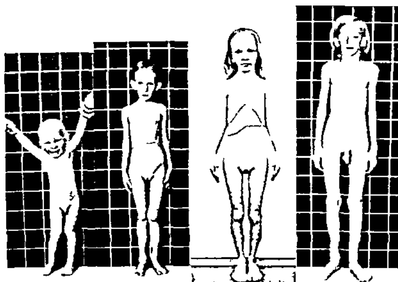


Fig 2

Four subjects with mulibrey nanism. Ages from left to right 26 months 8 12 and 15 years The second and fourth are siblings



Fig 3
Four subjects with mulibrey nanism Ages from left to right 5 11 18 and 21 years The older male had pericardial constriction with frank congestive heart failure The older female is the least typical of the series

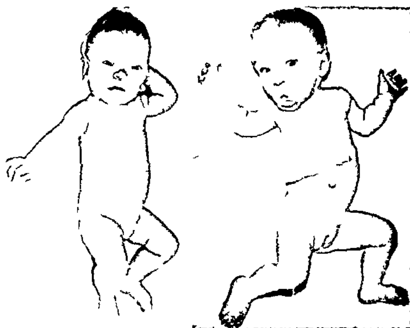


Fig 4
Two infants with mulibrey nanism ages 18 weeks and 13 months The younger girl (on the left) had cardiac failure from birth and died

a slightly increased basilar angle The long bones were thin with a relatively thick cortex and very narrow or almost obstructed medullary channel in all but three of the patients Seven had fibrous dysplasia of a tibia the lesion varied from a small subperiostal cyst to a large progres-

sive tumour which led to repeated fractures and pseudoarthrosis Cutaneous naevi flammei were frequent enough to be characteristic of the syndrome

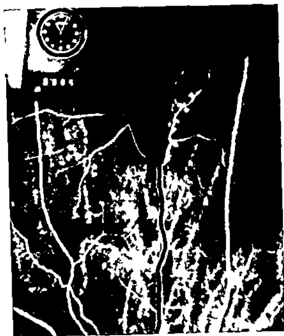
Besides prominent veins an enlarged liver was a constant component of the syndrome in five patients the liver edge was at least 5 cm below the costal margin in the right midclavicular line (Fig 4) In contrast to the peripheral signs of congestion definite enlargement of the heart was found in only two of the patients in the others the size of the heart was at the upper limit of normal or was slightly enlarged Pericardial calcium deposition was observed in the radiographs of two patients The electrocardiograms and catheterization findings were also compatible with pericardial constriction which was in fact proved in four patients at operation and in two at autopsy Myocardial fibrosis was observed in three of these cases and the scar of an old infarct was found in the posterior wall of the left ventricle in the girl who died at 1 3 years of age

Ophthalmological findings

Twenty three of the patients were studied by the ophthalmologist Visual acuity and refraction were determined and biomicroscopy and ophthalmoscopy were performed Electroretinography was done in three selected patients and fundus photography and fluoresceinangiography were performed in 11 patients

Visual acuity was normal in all but one child who had strabismic amblyopia Alternate esotropia was diagnosed in three children and exotropia in two adult sisters Most patients were emmetropic hyperopia ≧ 15 D was recorded in five patients and a female was myopic Biomicroscopy was normal The fundoscopic appearance was characteristic in 22 of the 23 patients in the whole series The optic disc and macula were normal but the retina had a reduced lustre Scanty pigmentation with dispersion and small clusters of pigment especially of the midperiphery as well as yellowish dots were the typical findings (Fig 5 a b) On fluorescein angiography the choriocapillaris was appreciably reduced even in the central part of the fundus (Fig 6) but especially in the mid periphery (Fig 7) Drusen were present in all but one of the 23 patients examined Fluoresceinangiography in general anaesthesia was not carried out in this patient The ERGs were normal None of the patients who cooperated on perimetry had changes of the visual field and none complained of adaptation disorders

a



b

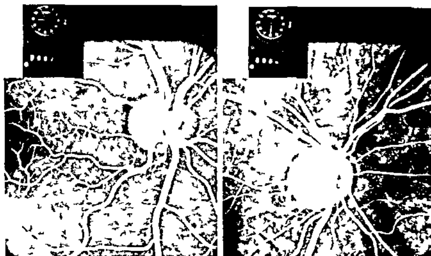


Fig 6

Fluorescein angiography of the optic disc and peripapillary area Marked hypoplasia of the choroid in mulibrey nanism (right) as compared with a normal fundus pattern of child of the same age (left)



Fig 7

Drusen and hypoplasia of choroid in midperiphery of fundus in a girl aged 14 with mulibrey nanism

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Fig 5 a and b

a) Fundus in mulibrey nanism in a boy aged 17 Drusen and scarce pigment with dispersion and clusters of the midperiphery b) Hypoplasia of the choroid drusen along venule in midperiphery

Discussion

Ocular manifestations have previously been described in syndromes of growth failure Rosenthal *et al* (1972) found peripheral lattice degeneration and cystoid degeneration of the retina as well as pigment prolifera tion in patients with spondyloepiphyseal dysplasia These authors also drew attention to ophthalmological findings in achondrodysplasia hypopituitary dwarfism diastrophic dwarfism and cartilage hair hypoplasia In all of these the finding was mainly of anomalies of the chamber angle

In our series of patients with mulibrey nanism the changes were quite different hypoplasia of the choroid scattered drusen and pigment changes These changes seem to be present at birth as they were found in the youngest patients as well as in the older ones Drusen are thought to originate from changes in the pigment epithelium (Hogan and Zimmerman 1972) They are situated in Bruch s membrane From our series of fluorescein angiograms we conclude that the pigment changes are secondary whereas the drusen seem primary changes affecting tissues of mesodermal origin The essential ocular changes in mulibrey nanism were hypoplasia of the choroid and drusen of Bruch s membrane No evidence of involvement of the receptors was found The normal ERG ruled out tapetoretinal degeneration The changes found somewhat resemble the normal ageing process The pattern of familial occurrence and regional concentration of the patient s ancestors in Finland very strongly suggests inheritance of mulibrey nanism by an autosomal rece sive gene (Perheentupa *et al* 1973 b) Of the components of the syndrome the involvement of the heart muscles and skeleton is most clearly primary As these tissues are mesodermal in origin a primary defect in that germ layer is implied though involvement of the other two layers cannot be excluded (Perheentupa *et al* 1973 b)

The involvement of the eyes and brain might also be caused by a primary mesodermal defect as the choroid and the meninges are of mesodermal origin The working hypotesis is that mulibrey nanism is caused by a mutation affecting an enzyme or structural protein which is predominantly active or produced by cells of mesodermal origin (Perheentupa *et al* 1973 b)

Our series of patients shows that the fundal changes are remarkably constant Mulibrey nanism should probably not be excluded if such changes are not found but their presence is strong support of the diagnosis Careful fundoscopy is necessary as the changes are most

frequent in the midperiphery and the central fundus may appear virtually normal thus changes were noted in only five of the 13 of our patients who had previously been studied by an ophthalmologist

References

Hogan M J & Zimmerman L E (1962) *Ophthalmic pathology* 2nd ed Saunders Philadelphia

Perheentupa J Autio S Leisti S & Raitta C (1970) Mulibrey nanism dwarfism with muscle liver brain and eye involvement *Acta paediatr Scand 59* 74—75

Perheentupa J Autio S Leisti S Raitta C & Tuuteri L (1973) Mulibrey nanism Review of 23 cases of a new autosomal recessive syndrome *Birth defects* original article series (in press)

Perheentupa J Autio S Leisti S Raitta C & Tuuteri L (1973 a) Mulibrey nanism *Scand J Clin Lab Invest 31* Suppl *130 21*

Perheentupa J Autio S Leisti S Raitta C & Tuuteri L (1973 b) Mulibrey nanism an autosomal recessive syndrome with cardiopathy *Lancet I* (in press)

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ACTA OPHTHALMOLOGICA
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*Department of Ophthalmology and the Children s Hospital
University of Helsinki Finland*

CORNEAL DYSTROPHY ASSOCIATED WITH A VARIANT OF MUCOPOLYSACCHARIDOSIS

BY

ANTTI VANNAS and VEIKKO NÄNTÖ

To be published elsewhere

Discussion

A Ansèth I would suggest the possibility of endothelial dysfunction as the cause of corneal edema with increasing opacification of the corneal stroma As dermatan sulfate was not found in the urine of the patient it would be of interest to see if this glycosaminoglycan is present in the corneal stroma if keratoplasty is going to be performed. Dermatan sulfate in the corneal tissue removed from the patient would make endothelial dysfunction a more plausible explanation for the corneal disorder described in this case

A Vannas The urine analysis might point to some disorder of the mucopolysaccharides Keratoplasty is planned to this poor child The study is going on

ACTA OPHTHALMOLOGICA
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Turku Finland 13–16 June 1973

Department of Ophthalmology and the Children s Hospital
University of Helsinki Finland

NEURONAL CEROID LIPOFUSCINOSIS OF EARLY ONSET

BY

C RAITTA and P SANTAVUORI

Published in Acta Ophthalmologica under the title Ophthalmological findings in infantile neuronal ceroid lipofuscinosis Acta Ophthalmol (Kbh) 51 755—763 1973

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XXI MEETING OF NORDIC OPHTHALMOLOGISTS
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Department of Ophthalmology and Children's Clinic
University of Helsinki Helsinki

GYRATE ATROPHY OF THE CHOROID AND RETINA WITH DEFECTIVE ORNITHINE METABOLISM

BY

KIRSTI TAKKI and OLLI SIMELL

Published in Lancet I 1031—1033 1973

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13—16 June 1973

The University Eye Clinic
Odense Sygehus Denmark

GONIOTOMY IN CONGENITAL GLAUCOMA

BY

P M MØLLER

Over 6 years in Odense Denmark we have seen 31 patients with con genital glaucoma 21 of these patients (32 eyes) were under 1 year old at admission to the eye clinic

30 eyes were subjected to operation all receiving a goniotomy a.m Worst as an initial operation

Table I
Congenital glaucoma patients in Odense 1967—1973 (31 patients)

	Number of eyes	
Goniotomy as initial operation	30	20 Goniotomies only 10 combined operations
Without operation	2	
Total	32	

Tension was restored to normal with goniotomy in 20 of these eyes 10 eyes needed further procedures for them to be restored to normal

It was often found necessary to carry out further goniotomies as the tension increased after a period of normal tension up to one year after the first goniotomy

We succeded in restoring the tension to normal in 90 % of the cases

Table II

	Number of eyes		Normal tension at follow up
Goniotomies only	20	8 eyes 1 goniotomy only 12 eyes > 1 goniotomy	20
Goniotomy + fistula formation	10	5 eyes trabeculotomy 5 eyes Elliot operation	7 (failed 3)
Without operation	2		2
Total	32		29

Table III
29 eyes with normalized tension

Papilla at admission	excaved	15
	normal	14
Papilla at follow up	excaved	10
	normal	19

As have other investigators we found that the papilla which at the first examination was excavated was now normal at follow-up This applied to 5 eyes out of the 29 eyes with normal tension

References

Shaffer R N & Weiss D I (1970) Congenital and pediatric glaucoma C V Mosby Co Saint Louis

Worst J G F (1966) *The Pathogenesis of congenital glaucoma* Royal Vangorcum Assen Netherlands Charles C Thomas

Discussion

S Vannas I congratulate Professor Møller for the fine results Since 10 years we have performed a modified goniopuncture for congenital glaucoma in Helsinki (Acta ophthal (Kbh) 1971 *49* 159—164) The results were good after the first operation in 70 per cent Due to its effectiveness we still do this procedure as the first operation but as the subsequent procedure if necessary the trabeculotomy

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
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CONGENITAL CATARACT MATERIAL

BY

M DAVANGER and S SPETALEN

Will be published in extended form later on

ACTA OPHTHALMOLOGICA
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CONCENTRATION OF AMINO ACIDS IN AQUEOUS HUMOUR AND PLASMA IN CONGENITAL CATARACT OR DISLOCATION OF THE LENS

BY

N EHLERS and F SCHØNHEYDER

The concentration of amino acids in aqueous humour and plasma was measured by ion exchange chromatography in six patients with congenital cataract or dislocation of the lens Case 1 with homo cystinuria and central cataract showed raised concentrations of methionine and glycine in the aqueous humour Case 2 with total cataract had an abnormal ratio between the aqueous and plasma concentrations of glutamic acid Case 3 also with total cataract had abnormal ratios for α aminobutyric acid isoleucine and leucine Case 4 with zonular cataract showed no abnormalities Cases 5 and 6 with dislocation of the lens had low concentrations of glycine in the aqueous humour The average values for 30 patients (mainly adults) are presented for comparison and the findings are discussed

When the concentration in the aqueous humour of some amino acids is maintained at a level different from that of the plasma (whether higher or lower) it primarily results from transport processes in the ciliary epithelium However amino acids are also transported from the aqueous humour into the lens where they are used for synthesis of proteins Amino acids may also reach the aqueous humour from the lens and an exhange may take place with the iris and with the cornea

Proteins constitute an unusually large percentage of the lens and cataract formation is linked to changes in the proteins (Kuck 1970) In

experimental galactose cataract amino acid uptake by the lens as well as protein synthesis, are affected We have therefore studied the concentrations of amino acids in the aqueous humour and the plasma in some patients with congenital cataract As dislocation of the lens is caused by defect zonular fibres composed of proteins cases of this disorder have been included in the study

Case material

Case 1 A girl born January 14 1971 who died April 4 1973 Birth weight 1550 g otherwise a clinically normal child except for bilateral central cataract The corneae were clear and of normal size Pupils were round the iris vessels were distinct and extended in loops onto the surface of the right lens The peripheral iris appeared thin and slightly pigmented Both lenses showed central irregular white opacities and vacuoles close to the anterior capsule (Fig 1) In the periphery of the cataract vacuoles were seen The peripheral lens was clear The tension was 5 0/5 5 g (Schiøtz) The chamber angle was covered by a grey membrane Ophthalmoscopy showed a peripheral red reflex from both eyes Both eyes were operated on by discission and aspiration. Ophthalmoscopy in October 1972 showed a somewhat pale but not definitely pathological right disc The vessels and macular region were normal The diagnosis of homocystinuria was verified on several occasions (Table III) and was supported by the autopsy findings This case will be reported later in detail with the full pathological findings The ocular findings comprised thick PAS-positive membranes on the ciliary processes and cystic degeneration of the retina (Figs 2 and 3)



Fig 1
Case 1 Homocystinuria and central cataract

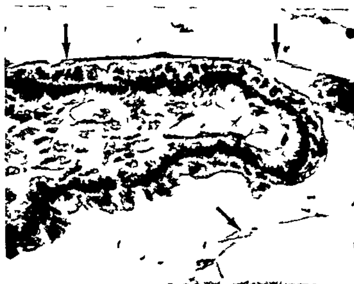


Fig 2
Case 1 Homocystinuria Ciliary epithelium covered by thick PAS positive membrane



Fig 3
Case 1 Homocystinuria Cystic degeneration of peripheral retina

Table I
Concentration of amino acids in aqueous humour Values in μmol/ml

	Case 1 CS			Case 2 OLJ	Case 3 LP	Case 4 LNM	Case 5 MV	Case 6 JE	Case 7 AJ	Average
	16 Months	19 Months	21 Months	6 Months	3 Years	7 ½ Years	5 ½ Years	8 Years	10 Months	30 patients
Taurine	0 022	0 017	0 035	0 047	0 048	0 045	0 038	0 031	0 038	0 066
Threonine	0 108	0 092	0 132	0 089	0 060	0 144	0 120	0 135	0 074	0 128
Serine + Glutamine	0 870	0 792	0 848	0 594	0 673	0 697	0 798	0 814	0 638	0 8[illegible]4
Glutamic Acid	0 017	—	0 008	0 014	0 012	0 013	0 017	0 011	0 012	0 009
Proline	0 074	—	0 046	0 064	trace	0 0[illegible]6	trace	0 033	0 035	0 044
Glycine	0 117	0 126	0 097	0 058	0 020	0 016	0 011	0 008	0 211	0 024
Alanine	0 208	0 149	0 [illegible]67	0 222	0 253	0 214	0 208	0 355	0 248	0 306
½ cystine	0 019	trace	trace	0 033	trace	0 018	trace	trace	trace	0 014
α ANBA	0 022	—	0 016	0 047	0 016	0 056	0 040	0 029	0 023	0 031
Valine	0 309	0 167	0 172	0 364	0 297	0 391	0 329	0 332	0 258	0 285
Methionine	0 127	0 109	0 084	0 036	0 028	0 057	0 036	0 043	0 035	0 044
Isoleucine	0 071	0 040	0 038	0 117	0 064	0 086	0 084	0 066	0 061	0 065
Leucine	0 117	0 086	0 059	0 211	0 132	0 183	0 186	0 154	0 129	0 139
Tyrosine	0 103	0 046	0 057	0 097	0 052	0 100	0 063	0 117	0 084	0 091
Phenylalanine	0 126	0 103	0 110	0 078	0 072	0 121	0 079	0 111	0 071	0 093
Urea	—	—	6 16	4 48	4 47	5 35	4 32	4 33	2 92	4 82
Lysine	—	—	0 116	—	—	0 129	0 147	0 154	0 136	0 159
Histidine	—	—	0 078	—	—	0 056	0 073	0 063	0 063	0 067
Arginine	—	—	0 100	—	—	0 069	0 117	0 110	0 071	0 105

Case 2 A 6 months old boy with bilateral congenital cataract of total type No aetiological diagnosis

Case 3 A 3 year-old boy with microphthalmos and bilateral congenital total cataract No aetiological diagnosis

Case 4 A 7½ year-old girl with bilateral zonular cataract No aetiological diagnosis

Case 5 A 5½ year old boy with bilateral dislocation of the lens upwards in the right downwards in the left eye left divergent squint normal ophthalmoscopy Left cranial scoliosis Clinical examination normal no Marfan s syndrome no mental retardation The urine did not contain homocystine

Case 6 An 8 year old boy with dislocated lenses upwards in the right downwards in the left eye and a right convergent squint with amblyopia Ophthalmoscopy normal normal intelligence no Marfan s syndrome At the age of two years homocystine was identified in the urine by two dimensional paper chromatography but the case was not further studied at that time At reexamination there was no homocystine in the urine The patient was given 100 mg 1 methionine per kg bodyweight and the urinary excretion of amino acids followed (Table III)

Case 7 A 2 months old boy with hyperglycinæmia There was no cataract and ophthalmo copy was normal

Biochemical findings

After cautious puncture of the anterior chamber 50—100 μl aqueous humour was withdrawn A sample of venous blood was taken simultaneously Both were examined quantitatively for amino acids by ion exchange chromatography using a Beckman Automatic Amino Acid Analyzer C The aqueous-humour amino acids were determined immediately after aspiration after suitable dilution with citrate buffer pH 2 2 The plasma was deproteinized immediately after centrifugation using a technique described by Stein & Moore (1954) In some cases amino acids were determined after loading with 1 methionine 100 mg per kg body weight

The concentrations of amino acids in the aqueous humour from the seven patients are presented in Table I together with average figures for 30 patients examined mainly adults (Ehlers & Schønheyder 1973) Apparently there are no age variations within childhood The values for glycine and methionine in case 1 and the value for glycine in case 7 are raised Cases 2 3 and 4 with congenital cataract probably show no abnormalities except possibly for the glycine concentration in case 2 In cases 5 and 6 with dislocation of the lens the concentration of glycine appears to be low

Table II shows the values for the ratios between the concentrations in aqueous humour and plasma in the cases studied Again the average

Table II

Ratios between concentrations in aqueous humour and plasma

	Case 1 CS			Case 2 OLJ	Case 3 LP	Case 4 LNM	Case 5 MV	Case 6 JE	Case 7 AJ	Average 30
	16 Months	19 Months	21 Months	6 Months	3 Years	7 ½ Years	5 ½ Years	8 Years	10 Months	patients
Taurine			1.46	0.070	0.69	0.52	0.54	0.50	0.54	1.02
Threonine			1.[illegible]2	1.03	1.13	1.15	1.58	1.02	1.40	1.17
Serine + Glutamine			1.07	1.19	1.38	0.99	1.12	1.37	1.62	1.25
Glutamic Acid			0.31	0.78	0.33	0.24	0.41	0.093	0.14	0.19
Proline			0.28	0.41	—	0.15	—	0.13	0.26	0.19
Glycine			0.23	0.39	0.13	0.063	0.057	0.033	0.22	0.109
Alanine			1.62	0.73	1.16	0.78	1.39	0.74	1.51	0.945
½ cystine			—	0.37	—	0.18	—	—	—	0.104
α ANBA			0.89	1.37	0.64	1.10	0.95	1.61	1.53	1.44
Valine			1.54	1.28	1.05	1.71	1.29	1.45	1.43	1.35
Methionine			2.89	1.80	1.65	2.32	2.77	2.39	3.50	2.54
Isoleucine			1.00	1.09	0.70	1.46	1.11	1.20	1.03	1.30
Leucine			1.12	1.17	0.87	1.65	1.22	1.[illegible]8	1.18	1.42
Tyrosine			1.90	1.56	1.61	2.22	1.91	2.21	1.95	1.84
Phenylalanine			2.44	1.42	1.71	2.37	1.80	2.09	2.45	2.01
Urea			0.91	0.76	0.64	1.03	0.99	0.87	0.78	0.88
Lysine			0.55	—	—	0.67	1.08	0.65	0.95	0.64
Histidine			1.15	—	—	0.84	0.97	0.90	1.24	0.85
Arginine			2.00	—	—	1.23	2.17	1.47	1.78	1.50

Table III

Excretion of methionine and homocystine after loading with 100 mg g methionine per kg body weight given at zero time (figures excretion in nmol/mg N) Three normal children under 3 years old were examined in the same manner In two no homocystine appeared in the urine in the third 0 15 nmol/mgN was excreted in the period 2—7 hours after loading

	Case 1 Congenital cataract		
		Methionine	Homocystine
Exp 1	Before loading	6 50	0
Age 2 y	3—4 1/2 h	34 0	15 0
	4 1/2—7	28 9	44 1
	15—19	30 4	38 4
	23—27	17 4	18 7
	27—31	10 0	4 9
Exp 2	Before loading	9 4	0
Age 2 y	0—4 h	42 0	9 4
	4—8	71 6	43 8
	8—12	52 4	41 0
	26—30	20 2	26 3
	30—34	12 8	24 5
	Case 6 Dislocation of the lens		
		Methionine	Homocystine
	Before loading	1 48	0
	0—1 h	4 10	0
	1—2	24 20	0 66
	2—3	16 68	0 61
	9—23	7 02	0 44

values for 30 patients are included for comparison In case 1 the ratio for methionine is not raised suggesting a normal transport mechanism in the blood-aqueous barrier In case 2 the ratio for glutamic acid is 2—4 times higher than in the other cases but still below 1 In case 3 the ratios for a-aminobutyric acid isoleucine and leucine appear to be abnormal In the other cases the ratio is well above 1 suggesting a concentration mechanism in the blood-aqueous barrier In case 3 these ratios are below 1 The figures for cases 4 5 and 6 probably show no abnormalities In case 7 with hyperglycinaemia the glycine ratio is still very low probably within the normal range

Methionine loading was carried out in cases 1 and 6 (Table III) In

fully raised (0 061 μmol/ml) The concentration of glycine was in both cases very low (0 003 and 0 008 μmol/ml)

The raised ratio C_{a_l}/C_{pl} for glutamic acid in case 2 may be remarkable Glutamic acid makes up a large proportion of the lens proteins and a raised ratio might indicate a reduced uptake by the lens Some reservations regarding this finding are however necessary as the conversion of glutamine to glutamic acid after the collection of the aqueous or plasma (Dickinson Rosenblum & Hamilton 1965) may alter the ratio

The apparently abnormal ratios for α aminobutyric acid isoleucine and leucine in case 3 cannot be explained at present

The findings in the case of zonular cataract (No 4) are probably normal which accords well with a temporary lesion in foetal life

The composition of human zonular fibres is not known In cattle they have a high content of cysteine and a low one of glycine and proline and almost no hydroxyproline (Buddecke & Wollensak 1966) The finding of a low concentration of glycine in the aqueous humour of cases 5 and 6 with dislocation of the lens cannot be explained Curtius *et al* examined the aqueous humour from a child with Marfan s syndrome The concentration of glycine was not reduced the proline concentration was normal and no hydroxyproline was present

Case 7 with hyperglycinaemia had no ocular abnormalities It was included as a natural loading experiment to demonstrate that the ratio C_{a_l}/C_{pl} for glycine is kept within the normal range despite enormous increase in concentrations

From these preliminary studies it appears that there may be abnormalities in the amino-acid metabolism in lens disorders Possibly the amino acids glycine and methionine are particularly affected an interesting suggestion as they are both maintained in the aqueous humour in concentrations different from that of the plasma methionine being higher glycine being much lower than in the plasma We intend to continue the studies in an attempt to characterize some of these disorders biochemically

References

Cagianut B (1957) Die freien Aminosauren in menschlichen Kammerwasser *Documenta ophthal* *11* 242—251

Cross H E & Jensen A D (1973) Ocular manifestations in the Marfan syndrome and homocystinuria *Amer J Ophthal* *75* 405—420

Curtius H C Martenet A C & Anders P W (1968) Bestimmung von freien Aminosauren im Augenkammerwasser des Menschen bei Homocystinurie Patienten und Kontrolfallen *Clin Chem Acta* *19* 469—476

Dickinson J E Rosenblum H & Hamilton, P B (1965) Ion exchange chromatography of the free amino acids in the plasma of the newborn infant *Pediatrics 36* 1—13

Ehlers N & Schønheyder F (1973) Free amino acids in aqueous humour of cataractous patients Association for Eye Research meeting Edinburgh 11—14 7 1973

Gaul G E & Gaitonde M L (1965) *Proc Int Nerochem Conf* Pergamon Press Oxford

Hanna C & Sanchez J (1972) Effects of acetazolamide on concentration of free amino acids in aqueous humour *Ophthal Res 3* 283—288

Kuck J F R (1970) In C N Graymore ed *Biochemistry of the eye* Chapters 3 4 and 5 Academic Press London

Mudd S H Levy H L & Grant M (1970) Deranged B_1 metabolism Effects on sulfor amino acid metabolism. *Biochem Med 4* 193—214

Presley G D & Sidbury J B (1967) Homocystinuria and ocular defects *Amer J Ophthal 63* 1723—1727

Stein W H & Moore S V (1954) The free amino acids of human blood plasma *J Biol Chem 211* 915

Wunderly C & Cagianut B (1954) Free amino acids in the human aqueous humour *Brit J Ophthal 38* 357—363

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INFLUENCE OF LOW BIRTH WEIGHT ON THE VISUAL ACUITY IN SCHOOL AGE

BY

HANS FLEDELIUS

300 children with a birth weight < 2000 g and 237 full-term controls were submitted to a usual clinic examination with a Snellen chart at a distance of 6 metres All children were 9—11 years old Glasses were offered and the best visual acuity determined binocularly as well as for each eye separately

Severe binocular visual handicap (< 3/60) occurred in only three children with retrolental fibroplasia and birth weight ≤ 1500 g Binocular visual acuity was ≥ 6/18 in the remaining 99 % of the low birth weight children as well as in all the full term children

Statistical analysis of the frequencies of the *whole* range of visual acuities showed that the low birth weight group scored significantly lower than the control group

(As part of a more extensive study the results are to be published in more detail later)

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CHRONIC CYCLITIS IN CHILDREN

BY

LAURI MERENMIES and AHTI TARKKANEN

In his textbook of 1889 Ernst Fuchs described chronic cyclitis as an independent syndrome Published reports state that the disease was very rarely diagnosed in the first half of the present century for no actual symptoms of inflammation are associated with it and there were few opportunities for clinical examination of the peripheral uvea and the pars plana region After developing scleral depression in 1950 as an aid in indirect ophthalmoscopy Schepens used the method to diagnose 27 cases of peripheral uveitis in which the syndrome matched perfectly that of chronic cyclitis Schepens and his colleagues subsequently carried out an extensive analysis of the syndrome in a case series of over 100 patients (Brockhurst et al 1960 1961 1968) In a group of 2500 patients with uveitis Hogan and Kimura (1961) found 100 cases of chronic cyclitis A significant number of the changes occurred in the area of the pars plana and hence the expression »pars planitis» has also been used (Wech *et al* 1960 Martenet 1964)

The syndrome is very characteristic there are no external symptoms of inflammation the patient sees an increasing number of swinging blurs in the field of vision and the vision is generally dimmed or a lowering of visual acuity is found on routine visual testing In the case series of Kimura & Hogan (1964) the vision was lower than 20/200 in 60 cases out

of 136 The illness occurred in children and in young adults the mean age being 27 and it was bilateral in 71 % of cases

In mild cases a misty blur is found in the front parts of the vitreous humour most of it near the ora and pars plana In moderate and severe cases there is an abundant exudation into the vitreous in the region of the ora usually in the lower parts and the area is covered by a white mass the »snow bank» formation Slezak (1969) distinguishes three forms the serous the infiltrative and the exudative Angiography reveals a leakage of fluorescein into the vitreous which suggests the presence of vasculitis in the syndrome When the disease persists focal changes are found and the blood vessels in the periphery of the retina become sheathed Another common change is oedema of the macula which Kimura & Hogan observed in 62 cases out of 136 A posterior subcapsular cataract occured in 36 Brockhurst & Schepens (1968) observed a detachment of the retina in 53 eyes in 105 patients suffering from peripheral uveitis Secondary glaucoma has also been a relatively common complication

Histological examination has been performed on only a few eyes in which the disease has mostly been at a late stage (Welch *et al* 1960 Brockhurst *et al* 1961 Kimura & Hogan 1964) the findings in the ciliary body were of non-specific inflammatory changes hyalinisation and fibrosis and perivascular inflammatory cell infiltration The last was also seen in the periphery of the retina Other changes were vitreous membranes cystic degeneration of the macula

Several recent surveys have discussed the aetiology and pathogenesis of chronic cyclitis but no common causal factors have been discovered (*e g* Schlaegel 1969 Mazow 1969 Maumenee 1970) Most of the patients have been free of other diseases The possible connection with multiple sclerosis (Breger & Leopold 1966 Giles 1970) or sarcoidosis (Martenet & Landolt 1964) has received no confirmation An investigation of the ultrastructure of the base of the vitreous suggested an immunological mechanism in cyclitis (Gartner 1971) We might repeat what was said in 1970 by Maumenee — that *»further clinicopathologic studies are greatly needed to determine the true pathogenesis of this process»*

During the past five years in the children s ward of the Eye Clinic of the University of Helsinki Central Hospital four boys of similar ages have been examined and treated after chronic cyclitis had been ascertained at routine eye examination (Table I) The ilness was bilateral in all three of them All showed exudation of vitreous in the region of the ora serrata and the pars plana usually in the lower half of the eye So far as complications were concerned oedema of the macula was found

Table I
Four children with chronic cyclitis

Case number	1	2	3	4
Sex	M	M	M	M
Age	9	10	11	11
Method of ascertainment	Routine examin at school	Routine examin. at school	Routine examin at school	Routine examin for glasses
Visual acuity	1 6/0 8	1 0/CF 1m	0 1/1 0	HM/0 6
Aqueous flare	—/+	—/+	+/—	—/—
Synechias	—/—	—/—	—/—	—/—
Posterior cort cataract	—/+	—/+	—/—	—/—
Peripheral vitr opacities	+/+	—/+	+/+	+/+
Snow bank at ora	+/+	—/?	+/+	+/+
Macular oedema	—/+	—/+	?/—	+/+
Retinal detachment	—/—	—/+	—/—	+/—
Cortisone glaucoma	+/+	—/—	+/+	—/—
Special findings (Laboratory X ray etc)	None	None	Strong positive tuberculin skin test	None

in all four eyes a posterior subcapsular cataract in two eyes and detachment of the retina in two The results of the investigations into aetiology proved negative In case No 3 a clearly positive Mantoux was found but no indications of manifest tuberculosis (The boy s father had suffered from pulmonary tuberculosis)

All the patients (Table II) received prednisone by mouth beginning with a single dose of 40—50 mg in the mornings every other day the duration of treatment depending on the development of the condition but averaging three months In Cases No 2 and No 4 treatment was resumed when an exacerbation of symptoms occurred after stopping the first treatment In two of the cases glaucoma developed during treatment this being kept under control with Asetazolamid and disappearing after treatment ended In Case No 4 the retinal detachment improved with surgical treatment This boy had a great number of membranous blurs in the vitreous but ruptures of the retina could not be found In Case No 2 partial detachment of the retina seemed to disappear during treatment but vision did not improve and the ERG became extinguished in this eye

Table II
Treatment and outcome of four children with chronic cyclitis

Case number	1	2	3	4
Follow-up years	2	3	5/12	4
Treatment	Oral and topical steroids	Oral steroids	Oral and topical steroids	Oral steroids
Treatment of cortison glauc	Acetazol-amide		Acetazol amide	
Surgery for ret detachment				Cerclage
Visual acuity				
— at diagnosis	1 6/0 8	1 0/CF 1m	0 1/1 0	HM/0 6
— at last visit	1 6/1 3	1 0/PL	0 3/1 6	0 4/1 0

The syndrome and the complications associated with it were typical and could be classified as moderately severe Except for one eye all the cases improved during oral prednisone treatment No common side-effects of steroids were caused by the treatment presumably because of the manner of dosage (single dose every second day)

In steroid treatment of chronic cyclitis sub-Tenon injections have generally been recommended (Kimura & Hogan 1964 Nozik 1972) This method of administration may be difficult in children (in our cases they were tried only once) Other local therapeutic measures such as dia thermy (Gills 1968) and cryo coagulation (Mazow 1969) may also be effective When the illness does not respond to steroids antimetabolites may be used such as Methotrexate (Wong & Hersh 1965) 6-Mercaptopurine (Newell & Krill 1966) Azathioprine (Newell 1967) Cyclophosphamide (Gills & Buckley 1970) of Chlorambucil (Hogan 1970) Hence treatment may be tailored to the individual syndrome

Summary

In four typical cases of chronic cyclitis in boys aged 9—11 the condition was bilateral in three The complications included macular oedema in 4 eyes posterior cort cataract in 2 eyes and retinal detachment in 2 eyes

one of these last-mentioned being succesfully treated surgically The changes healed partly or wholly on treatment with oral steroids The vision was lost in one eye only Investigations failed to reveal the aetiology of the condition

References

Breger B C & Leopold I H (1966) The incidence of uveitis in multiple sclerosis. *Amer J Ophthal 6? 540—545*

Brockhurst R J., Schepens C L. & Okamura I D (1960) Uveitis II Peripheral uveitis Clinical description, complications and differential diagnosis *Amer J Ophthal 49* 1257—1266

Brockhurst R J Schepens C L & Okamura I D (1961) Uveitis III Peripheral uveitis Pathogenesis etiology and treatment *Amer J Ophthal 51* 19—26

Brockhurst R J & Schepens C L (1968) Uveitis IV Peripheral uveitis The complication of retinal detachment *A M A Arch Ophthal 80* 747—753

Fuchs E (1889) Lhb d Augenheilk Leibzig (Textbook of Ophthalmology p 272 Appleton New York 189_)

Giles C L (1970) Peripheral uveitis in patients with multiple sclerosis *Amer J Ophthal 70* 17—19

Gills J P (1968) Combined medical and surgical therapy for complicated cases of peripheral uveitis *A M A Arch Ophthal 79* 723—728

Gills J P & Buckley C E (1970) Oral cyclophosphamide in the treatment of uveitis *Trans Amer Acad Ophthal Otolaryng 74* 505—508

Gartner J (1971) The fine structure of the vitrous base of the human eye and pathogenesis of pars planitis *Amer J Ophthal 71* 1317—1327

Hogan, M J in discussion of Gills J P & Buckley C E 19 0

Hogan M J & Kimura S J (1961) Cyclitis and peripheral chorioretinitis *A M A Arch Ophthal 66* 667—677

Kimura S J & Hogan M J (1964) Chronic cyclitis *A M A Arch Ophthal 71* 193—_01

Maumenee A E. (1970) Clinical entities in uveitis an approach to the study of intraocular inflammation *Amer J Ophthal 69* 1—27

Martenet A C (1964) A new term in uveitis pars planitis *Ophthalmologica 147* 282—?90

Martenet A-C & Landolt E (1964) The importance of the Kveim test in the etiological research on peripheral uveitis *Bull Soc franc Ophthal 77* 604—611

Newell F W (1967) Treatment of uveitis with Azathioprine (Imuran) *Trans Ophthal Soc U.K 87* 449—551

Newell F W & Krill A E (1966) The treatment of uveitis with 6 Mercaptopurine *Amer J Ophthal 61* 1250—1255

Nozik R A (1972) Periocular injectio of steroids *Trans Amer Acad Ophthal Otolaryng 76* 695—?05

Slezak H (1969) Peripheral uveitis Clinical presentation, pathogenesis and differential diagnosis *Fortschr Med* 87 209—210
Welch R B Maumenee A. E & Wahlen, H E (1960) Peripheral posterior segment inflammation vitreous opacities and edema of the posterior pole Pars planitis *A M A Arch Ophthal* *64* 540—549
Wong V G & Hersh E M (1965) Methotrexate in the therapy of cyclitis *Trans Amer Acad Ophthal Otolaryng* *69* 279—294

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DRUSEN OF THE OPTIC DISK ON CHILDREN

BY

H ERKKILÄ

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TREATMENT OF A CASE OF SYMPATHETIC OPHTHALMIA

BY

E GOLDSCHMIDT and J LOCHTE

Today sympathetic ophthalmia is rare in the Scandinavian countries Thus in the Ophthalmic Pathology Laboratory in Copenhagen only one definite case was found during the 10-year period 1958—1967 in a total of 276 eyes enucleated for trauma (Jensen 1968)

Sympathetic ophthalmia has a poor prognosis and in earlier case series at best half the patients have had a final visual acuity of 6/60 or better Steroids have altered the prognosis but even they have not always prevented the continual recurrence of uveitis in the sympathized eye This article describes briefly some other methods of treatment which may be used when conventional steroid therapy seems insufficient

Case report

A boy now aged 7 sustained a right sided contusion at the age of 3½ years (in 1969) Two months later he was found to have phthisis of the right eye with preservation of perception of light a dislocated lens and connective tissue masses behind the lens The boy was not photophobic but there was a moderate aqueous flare in the anterior chamber and the eye was soft

During the subsequent two years he was frequently seen by an ophthalmologist and exenteration was contemplated on several occasions In April 1972 i e 2½ years after the contusion wispy iritis appeared in the left eye and the right eye was enucleated Microscopic examination showed considerable lymphocytic infiltration in the uveal tissue with granulomas of epithelioid cells and giant cells

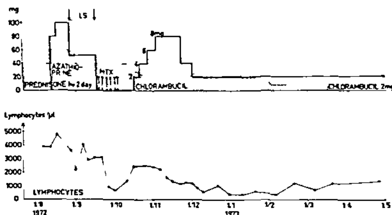
some of the nuclei contained melanin granules Thus the microscopic findings were characteristic of the changes seen in sympathetic ophthalmia Definite Fu hs nodules were not seen but there were numerous dru en

Treatment

During the first 3 months after enucleation the boy was treated with mydriatics and steroids locally as well as dexamethasone 0 5 mg subconjunctivally daily or every other day and prednisolone 10—60 mg daily Though condition fluctuated considerably in severity the visual acuity remained at normal levels In August 1972 treatment had to be intensified owing to an increasing aqueous flare and decreasing ocular tension For this reason immunosuppressants were also used (see Figure) Azathioprine (Imurel) 3 mg/kg daily was supplemented in 3 weeks with antilymphocyte serum 10 ml daily Nevertheless this too failed to improve the condition of the eye as did 4 weeks metrotrexate therapy (MTX on the figure) 25 mg/m² intravenously every 5th day

By now the boy was quite Cushingoid and had arterial hypertension so that the dose of steroid was reduced His general condition and longitudinal growth were entirely unaffected throughout From the middle of October he was given chlorambucil (Leukeran) in rising (later falling) doses and Kenalog subtenonially every 2—3 weeks

Gradually his condition improved and the dose of prednisolone could be tailed off but not completely discontinued until March 19 1973 During the entire period Ultracortenol drops were given topically and various



mydriatics were also used when a definite aqueous flare or a tendency to synechiae was present

The ocular tension remained normal until April 1973 when it rose slightly affecting the optic nerve but there were no visual-field defects The tension was controlled by Diamox 125 mg 3 times daily

Present status Visual acuity about 6/12 Tension normal on the above mentioned treatment A posterior cortical cataract is visible in the lens There is no aqueous flare, and only very little reaction in the vitreous

The boy is still receiving chlorambucil 2 mg daily

Discussion

The aetiology of sympathetic ophthalmia is still puzzling but various findings indicate that it should be classified as an autoimmune disease (Allansmith & O Connor 1970) This is also suggested by the effect — though inconstant — of steroids and other immunosuppressants In the present case it is difficult to conclude which of the individual components of the treatment was the most effective

The figure shows that the use of chlorambucil by mouth coincided with improvement At the same time concentrated steroids were injected subconjunctivally or subtenonially and this mode of administration was thought to have been of the most importance in reducing the aqueous flare and the intraocular reaction as a whole

Other authors have reported successful treatment with these drugs at an earlier stage of the disease process Antilymphocyte serum which is not generally available is costly and involves some risks which however are decreasing with the ever-increasing purity of the agent Fuchs (1969) observed that they had a dramatic effect in a 13-year-old boy but we could not reproduce this effect

Metrotrexate has also been reported to be effective If the lymphocyte count is any index of the efficacy of this treatment, perhaps we did not administer it for long enough Certainly during chlorambucil therapy which was accompanied by improvement (cf the figure) the lymphocyte count remained depressed for a long time but we are unjustified in concluding that there is causal relationship

In all forms of immunosuppression it is impossible to demonstrate the specific factor — be it lymphocytes or immunoglobulin components — which the doctor is aiming to suppress We did not follow the immunoglobulin levels in this boy

On the other hand we did do intensive checks on the formed elements of the blood All these measures as well as the actual doses of the drugs and the management of side effects must be decided on in collaboration with departments having experience in these fields

We are continuing this treatment we hope with an eventual good result

References

Allansmith M R & O Connor G R (1970) *Survey Ophthal 14* 367—402
Fuchs J (1969) *Klin Mbl Augenheilk 154* 777—785
Jensen, O A. (1968) *Acta ophthal (Kbh) 46* 1194—1206

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RETROSPECTIVE STUDY OF 117 PATIENTS WITH OPTIC NEURITIS

BY

E. NIKOSKELAINEN and P RIEKKINEN

117 patients followed for 3 to 23 years after an initial bout of optic neuritis were examined to clarify the prognosis for sight and for multiple sclerosis 97 (84 %) of patients were aged between 20 to 49 years during the onset of optic neuritis In 51 patients both optic nerves were affected Bilateral papillitis was a common manifestation, especially in children. Recurrent optic neuritis occured in 26 % of patients On general criteria 49 6 % were diagnosed as having probable multiple sclerosis and 19 7 % as possible multiple sclerosis On ophthalmological re examination the prognosis for sight was good in 64 % of eyes but 19 % of eyes had poor vision under 0 1 On the other hand perimetry showed that despite good central visual acuity there was often a visual field defect The most common late finding was enlargement of the blind spot and/or paracentral nerve fibre bundle defect (30 %) many eyes also had permanent central or caecocentral scotoma (27 %)

Key words optic neuritis — optic atrophy — multiple sclerosis — Leber's hereditary atrophy — perimetry

Optic neuritis is a fairly common condition the most important cause being multiple sclerosis Although at its onset visual acuity is often decreased considerably most patients recover within a few weeks For

the reason we usually know little about the prognosis of our patients Several reports have dealt with retrospective studies of patients with optic neuritis For example Taub and Rucker (1954) suggested that an individual patient of age 20 to 44 years has a 40 to 50 % change of having multiple sclerosis In a series of 148 cases with optic neuritis followed up between six months and seven and a half years Rose (1970) showed that 76 % had some evidence of multiple sclerosis

Our study was part of a larger study to clarify the prognosis for sight and for multiple sclerosis in 117 patients seen between 1950 and 1960 at the University Hospital of Turku This is a preliminary report and both neurological and ophthalmological aspects of this re-examination will be reported later in more detail

Methods

At re examination the patients were questioned about their medical history especially about all neurological symptoms Careful neurological and ophthalmological base line examinations was performed including perimetry with Goldman s perimeter

Results

Fig 1 shows the age distribution of the case series Most patients (84 %) were between 20 and 49 years at the onset of optic neuritis There were 67 women and 50 men Eight patients were under 15 years of age at the

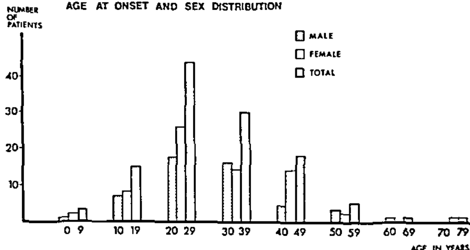


Table I
Data on the retrospective study of 117 patients with optic neuritis

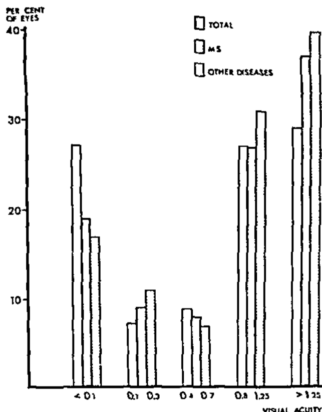
	Number of patients	Per cent
Unilateral optic neuritis	66	56 4
Bilateral optic neuritis more than 3 months interval	15	12 8
Bilateral optic neuritis less than 3 months interval	36	30 8
Total	117	100 0 %

Table II
Aetiology of optic neuritis in 117 re examined patients

	Number of cases	Per cent	
Probable multiple sclerosis	58	49 6	MS group
Possible multiple sclerosis	23	19 7	69 3 %
Leber s disease	6	5 1	
Infectious disease	5	4 3	
Other definite cause	7	5 9	
Unknown	18	15 4	
Total	117	100 0 %	

onset of disease Except one case with unilateral papillitis all of these patients had a bilateral papillitis Sixty-six patients had unilateral and fifty-one bilateral optic neuritis (Table I) If we consider bilateral optic neuritis with an interval of more than three months as a new bout 26 % of patients had recurrent optic neuritis Fifteen patients showed at least three bouts of optic neuritis Strikingly, several patients reported symptoms even years after acute optic neuritis transient pain on movement of the eye or a sudden blurring of vision especially when the body temperature rose For example the Finnish Sauna caused blurring of vision in many patients This feature which is known as Uthof s sign was more common among patients with multiple sclerosis

In this series half the eyes with optic neuritis had a normal optic disc at the onset of the disease and were classified as having retrobulbar optic neuritis 23 % had classical papillitis with papilloedema often also with haemorrhages of the disc Other eyes had borderline abnormalities such as hyperaemia or blurring of the disc sometimes associated with haemorrhages but without papilloedema



Using international diagnostic criteria of multiple sclerosis on the basis of medical history and neurological re examination 49.6 % of patients were diagnosed as having probable multiple sclerosis and 19.7 % of patients as having possible multiple sclerosis (Fig 2) Two of our eight cases with optic neuritis during childhood probably had multiple sclerosis and another two cases possibly had this disease In 69 % of patients with multiple sclerosis optic neuritis was the first symptom and this caused admission to hospital

Eight patients had Leber's hereditary optic atrophy All patients except one were related to one other One of the patients was a woman whose disease had begun with acute bilateral papillitis but had then recovered showing after a 3-year follow up a normal visual acuity in both eyes and only slightly enlarged blind spots in visual fields In seven other cases the prognosis for vision was bad leaving vision under 0.1

Table III
Visual field findings in 165 re examined eyes with optic neuritis

Visual field	Number of eyes	Per cent
Normal	55	33 3
Enlarged blind spot and/or paracentral nerve fibre bundle defect	50	30 1
Nerve fibre bundle defect involving fixation and periphery	2	1 2
Central and caecocentral defects	44	26 6
Peripheral defects	9	5 5
No field (with isopter IV/4)	5	3 3
Total	165	100 0 %

bilateral central scotomas and total pallor of both discs The cause of the optic neuritis was infectious in 3 cases upper respiratory infection sinuitis and meningitis in childhood Other aetiological causes were vascular disturbance (2) chronic alcoholism (1) Guillain-Barre syndrome (1) subacute combined degeneration (1) collagenosis (1) and chronic renal insufficiency (1) In 18 patients the aetiology could not be determined The ophthalmological re examination showed that in 64 % of the eyes with optic neuritis the visual acuity was good or excellent (Table III) However 19 % of the eyes had vision of under 0 1 The prognosis for vision in patients with multiple sclerosis corresponds roughly with that of the total case series though possibly the prognosis for vision is slightly be*ter Among the patients with causes other than multiple sclerosis the prognosis is again much the same as in the case series in general The proportion of eyes with poor visual acuity (under 0 1) was however exceptionally high owing to the large group of those with Leber s disease and some other cases with bilateral optic neuritis without recovery The re-examination of visual fields gave interesting results showing that despite good visual acuity they were often defective Thus only 33 3 % of eyes with a history of optic neuritis had the visual field recovered to normal The most common finding was an enlarged blind spot or a para central field defect or both The patients had usually not noticed such defects In 26 6 % of the eyes there was apparently a permanent central or caecocentral scotoma In some cases the scotoma was only relative and occasionally the central defect was associated with peripheral contraction Two eyes had nerve-fibre bundle defects involving both fixation and periphery only peripheral defects could be found in 9 eyes

with a history of optic neuritis Five eyes were blind thus making perimetry impossible Two patients with MS had such a high disability that perimetry was not possible

In the whole series 30 % of eyes had temporal pallor or slight total pallor of the disc 32 % were totally pale after optic neuritis The appearance of optic disc did not always correlate with visual acuity but correlated better with the visual field findings Abnormal visual fields were usually associated with pathological changes in the optic discs

Discussion

The prognosis for multiple sclerosis we found corresponds to that found by Rose (1970) In both reports the percentages are somewhat higher than in the literature Long follow-up period careful knowledge of the medical history and neurological re-examination enabled us to identify cases with benign disease Many of these patients with benign disease never spontaneously visit a neurologist Multiple sclerosis seems to be commoner than is usually reported but only the patients with greater disability are seen by the neurologist Moreover probably the type of the disease which affects mostly the optic nerves the dorsal half of the brainstem or the posterior columns is more benign than other types of the disease In 69 % of our patients with multiple sclerosis the optic neuritis was first symptom which caused the admission to hospital Some of these patients had however had earlier minimal symptoms that were possibly the first sign of the disease For example transitory paraesthesiae or weakness in a limb give often rise to such slight subjective symtoms that the patient does not visit a doctor Conversely acute optic neuritis with a sudden reduction in visual acuity often associated with pain on movement or palpation of the eye is so triking a symptom that most patients visit an ophthalmologist immediately

Usually optic neuritis is classified into retrobulbar neuritis and papillitis We suggest that this strict division is inadequate because there is a large group of borderline cases showing a blurred or hyperaemic disc sometimes associated with haemorrhages In our series 27 % were such borderline ca es In our eight patients with optic neuritis during childhood the common manifestation was bilateral optic neuritis together with papilloedema corresponding with earlier findings for example by Kennedy and Carrol (1960)

We found that the prognosis for sight was much the same as in other

Table I
Occurrence of eye inflammation in patients with Yersinia infection

Clinical group	Number of patients		
	Total	Uveitis	Episcleritis/ Conjunctiv
Acute arthritis	124	5	7
Erythema nodosum	127		6
Others	160	2	2
Total	411	7	15
Female	270	2	13
Male	141	5	2
Age range (years)		10—48	17—63

came from all parts of Finland The diagnosis of Yersinia infection was based on serological findings (Ahvonen 1972 a) In addition the corresponding Yersinia serotype was isolated from stools or other specimens in 121 cases One patient with conjunctivitis had Y pseudotuberculosis infection the other patients with eye inflammation had infections with Y enterocolitica serotype 3 or 9

Clinical observations

Table II shows some clinical and laboratory data of the 22 patients with eye inflammation associated with Yersinia infection The disease usually started with fever and diarrhoea or abdominal pain succeeded after about a week by arthritis or erythema nodosum The onset of episcleritis or conjunctivitis usually coincided with that of erythema nodosum or arthritis Uveitis appeared at any time during the first month of the disease The duration of the arthritis was usually less than six months that of erythema nodosum in most cases less than three weeks and that of uveitis one to three months

Uveitis was diagnosed in five patients with acute arthritis and in two other patients one of whom had ankylosing spondylitis and the other a history of a previous attack of arthritis In addition seven other patients with Yersinia arthritis had had one or two attacks of uveitis three months to three years after the Yersinia infection In most cases of uveitis the inflammation was limited to the anterior parts of the uvea (iritis) but in at least three cases it also involved the posterior part The clinical picture of uveitis did not differ from that of uveitis due to other causes The patients received the usual therapy for uveitis Antibiotics had no

Table II
Some symptoms signs and laboratory findings in cases of Yersinia infection and eye inflammation.

Symptoms signs lab findings	Number of patients	
	Uveitis	Episcleritis/Conjunctiv
Fever	5	14
Abdominal symptoms	4	14
Erythema nodosum		6
Acute arthritis	5	
X ray changes in sacroiliac joints	2	
ESR > 50 mm/h	4	12
Leucocytosis > 10 000/mm	3	6
Yersinia maximal aggl titre 320 20 000	7	15
Yersinia isolated		4
Total	7	15

definite effect on the course of uveitis arthritis or erythema nodosum Two patients with uveitis had one or two recurrences later

Since some of the 15 patients with episcleritis or conjunctivitis were not examined by an ophthalmologist in the acute phase it is not possible in retrospect to give the exact number of patients with either of these diseases However the hospital records and the histories of the patients show that episcleritis was usually associated with erythema nodosum and conjunctivitis with acute arthritis

In 12 out of the 22 cases a follow-up eye examination was performed three to six years after the acute phase The vision the visual fields and the ocular tension were normal in every case In two cases with an initial diagnosis of episcleritis distinctly more pigment was seen in the chamber angle of the affected eye than of the contralateral eye obviously a sign of mild irritation of the anterior uvea Appreciable pigmentation of the corneal endothelium was found in one case and marked pigment dust dispersion on the iris in one case Slight anterior or posterior opacity of the lens capsule was noted in three cases No significant functional sequelae were observed in the eyes

Discussion

The present series suggests that uveitis and conjunctivitis occur in association with Yersinia infection in some patients with acute arthritis and

episcleritis in some patients with erythema nodosum If properly treated the prognosis of the eye inflammation in these cases seems to be good but uveitis tends to recur The pathogenesis of uveitis and episcleritis like that of arthritis and erythema nodosum, is unknown at present Possibly immunological mechanisms and hereditary factors play a part Yersinia could not be isolated from the synovial fluid in our cases of arthritis Uveitis is common in patients with ankylosing spondylitis and two of the present patients with uveitis had radiological changes in the sacroiliac joints suggestive of this disease Possibly some of the other patients also will later develop ankylosing spondylitis as do many patients with Reiter s syndrome after Shigella infection Possibly these patients are particularly apt to contract uveitis

References

Ahvonen P (1972 a) Human yersiniosis in Finland I Bacteriology and serology *Ann clin Res 4* 30

Ahvonen P (1972 b) Human yersiniosis in Finland II Clinical features *Ann clin Res 4* 39

Knapp W (1968) Die Pseudotuberculose des Menschen Klinik Diagnose Therapie und Epidemiologie *Ther Umsch 25* 195

Mollaret H (1971) L infection humaine à Yersinia enterocolitica en 1970 à la lumiere de 642 cas récents Aspects cliniques et perspective epidémiologiques *Path et Biol 19* 189

Winblad S (1970) Yersiniainfektioner hos manniskan *Medicinisk Årbog 13* 244

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Aus der Augenklinik des Regionkrankenhauses Örebro
(Chefarzt Doc Med dr R Tornquist) Schweden

OPERATIVE BEHANDLUNG VON REZIDIVIERENDEN FEHLSTELLUNGEN DER LIDER MIT GLYCERINKONSERVIERTER SKLERA

VON

EIVIND WOLD

Für die Reoperation des rezidivierenden Entropium wird eine neue Methode beschrieben die die pathogenetischen Faktoren berücksichtigt Ein halbmondförmiges Stück glycerinkonservierter Sklera wird vor dem Tarsus unter leichter Anspannung am medialen Lidligament und am Periost des äusseren Orbitalrandes befestigt Eine Hebung und Streckung der Lidkante eine Verstärkung des Septum orbitale inferior und eine Stabilisierung des Tarsus in der Normalstellung wird erreicht Die Operationsmethode hat sich klinisch bewährt und wird empfohlen

Augenlidchirurgie — Entropium— Ektropium — Transplantation — Glycerinkonservierte Sklera — Gewebekleber

Zur Beseitigung von Stellungsabweichungen der Lider steht uns eine grosse Anzahl klassischer Operationsmethoden zur Verfügung Oft erlebt man aber dass diese Methoden nicht zu dauerhaftem Erfolg führen Bei der Wahl der Operationsmethode soll man besonders bei Rezidiven die Faktoren berücksichtigen die für das Zustandekommen der Fehlstellung bedeutungsvoll sind

Bei dem senilen Entropium des Unterlides sind die folgenden am wichtigsten

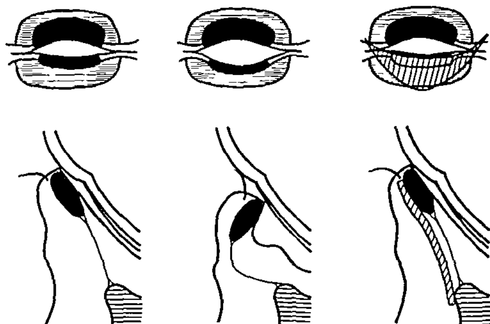


Abb 1

Palpebraler Stutzapparat (modif nach Hallermann) Links bei normaler Lidstellung und intakter Funktion Mitte bei Entropium mit Lockerung der Ligamenta palpebralia und Erschlaffung des Septum orbitale inferior Rechts nach Operation mit der Skleraplatte

1 Erschlaffung des Ligamentum palpebrale mediale und laterale mit reduzierter horizontaler Lidspannung und nach unten durchhangender Lidkante (Lohlein 1922 Bangerter 1969 Hallermann 1971) (Abb 1)
2 Erschlaffung des Septum orbitale inferior mit Vorwolbung von Orbitalfett und Vorschiebung der unteren Tarsuskante (Blaskovics 1922 Duke-Elder 1952 Jones 1963) (Abb 1)
3 Verschiebung der Fasern des Musculus orbicularis oculi in Richtung zur unteren Lidkante (Jones 1963) Blaskovics und Kettesy (1970) meinen dass die praetarsalen Muskelfasern gegen die Lidkante verschoben werden die dadurch nach innen gezogen wird Dalgleich und Smith (1966) haben experimentell gezeigt, dass die praeseptalen Fasern gegen die untere Tarsuskante verschoben werden die dadurch nach vorne und oben gedruckt wird

Eine oft altersbedingte Reduktion des Orbitalfettes die ein leichtes Zurucksinken des Bulbus bewirkt erleichtert moglicherweise das Auftreten der oben aufgefuhrten Faktoren (Lohlein 1922 Duke-Elder 1952 Jones 1963)

Das klinische Bild bei Rezidiven nach mehrfach vorausgegangenen Entropium Operationen ist charakterisiert durch eine auffallige Erschlaffung des ganzen Stutzapparates mit einer nach unten durchhangenden eingerollten Lidkante Oft ist die Haut am Lid und in der Schlafengegend unelastisch und nachgiebig (Lohlein 1922 Duke-Elder 1952) In diesen Fallen kann man mit den ublichen Entropium-Eingriffen kaum einen grosseren Effekt erwarten Goldmann (Zit in Fankhauser 1966) und Hallermann (1971) haben zu den Operationen nach v Blaskovics und Kettesy Modifikationen angegeben wonach eine zusätzliche Naht vom Tarsus zum Periost des ausseren Orbitarandes gefuhrt und nach leichter Anspannung geknotet wird Das Unterlid erfahrt hierdurch eine Straffung und Hebung Fankhauser (1966) hat um diesen Effekt zu erreichen einen 2 mm breiten glycerinkonservierten Sklerastreifen benutzt der an der unteren Tarsuskante und am lateralen Margo orbitalis befestigt wurde Diese Modifikationen beeinflussen aber nicht das Septum orbitale inferior und die praeseptalen Orbikularismuskelfasern und bewirken ausserdem eine einseitige Verschiebung des Tarsus nach lateral

Methodik

Fur die Reoperation des rezidivierenden Entropiums haben wir eine Operationsmethode entwickelt die die oben genannten Faktoren berucksichtigt Da bei dem Ektropium atonicum ebenfalls eine Insuffiziens des palpebralen Stutzapparates vorliegt haben wir die Methode auch in einigen solchen Fallen benutzt

Nach gebrauchlicher Lidanaestesie wird der Hautschnitt lidrandparallel ca 4 mm unterhalb der Wimperreihe gelegt Die Haut wird unterminiert bis zum Lidrand und bei Entropium werden eventuell noch ruckgebliebene praetarsale Muskelfasern entfernt Das Ligamentum palpebrale mediale und das Periost an der unteren und ausseren Orbitakante werden dann freigelegt Ein halbmondformiges Stuck Leichensklera ca 5 cm lang und 2 cm breit konserviert und verwahrt in 95 % steriler Glycerinlosung (King *et al* 1962 Fankhauser 1966) wird rehydriert und mit feinen Nahten oder mit Gewebekleber (Isobutylcyanoacrylat) am oberen und unteren Teil der Tarsusvorderseite befestigt Der mediale Sklerazipfel wird unter leichter Anspannung an das Ligamentum palpebrale mediale und der laterale Zipfel unter gleichzeitiger Spannung und Hebung an das Periost der ausseren Orbitakante stabil festgenaht Die freie untere bogenformige Sklerakante wird ohne jeglichen Zug an dem Periost der unteren Orbitakante mit ein paar Nahten befestigt Schliesslich wird der Hautschnitt vereinigt

Man erhalt mit dieser Methode die gewunschte Streckung und Hebung der unteren Lidkante Das Septum orbitale inferior wird verkstarkt der Tarsus wird in der Normalstellung stabilisiert und die Verschiebung der praeseptalen Orbikularismuskelarkaden nach vorne verhindert (Abb 1)

Ergebnisse

Zehn Lider sind mit dieser Methode operiert worden Wir haben glycerinkonservierte Sklera gewahlt da sie genugend Festigkeit und Steifheit besitzt gleichzeitig aber sehr geschmeidig ist Es ist auch ein leicht zugangliches Material das ohne Qualitatseinbusse in Glycerin bei Zimmertemperatur unbegrenzt haltbar zu sein scheint (Frankhauser 1966) Skleraltransplantationen sind seit Anfang der funfziger Jahre ausgefuhrt worden und die ausserordentlich gute Gewebsvertaglichkeit der Sklera ist wohl dokumentiert (Lister 1951 Paufique & Moreau 1953 Payrau & Remky 1961 Johnson et al 1962 Fankhauser 1966) Bei unseren Fallen haben wir keine Anzeichen einer postoperativen Inflammation oder Zeichen einer Abstossung gesehen In einem histologischen Preparat von *einem der Falle sieht man sechs Monate nach der Operation* die Sklera mit erhaltener Lamellenstruktur vollig eingeheilt ohne Zeichen einer inflammatorischen Reaktion

Bei vier Fallen von atonischem Ektropium war die Operation primar erfolgreich Zwei Falle haben jedoch nach 3 b z w 6 Monaten rezidiviert weshalb die Methode in ihrer jetztigen Form kaum Vorteile zu bieten scheint im Vergleich mit den Lidrand verkurzenden ublichen Ektropium Operationen

Das Ergebnis bei den Fallen mit senilem rezidivierenden Entropium ist ermutigender und geht aus der Tabelle I hervor Alle Patienten sind fruher mehrmals mit verschiedenen Methoden und Modifikationen operiert worden ohne dauerhaften Effekt Nach der Entropium Operation mit Sklera war der Verlauf in den meisten Fallen unauffallig In zwei Fallen (Nr 1 und 3) ist eine der Ligament-Nahte aufgegangen und das Lid ist nach unten gesunken Diese Komplikation kann wahrscheinlich vermieden werden indem man doppelte Nahte setzt oder indem man den Sklerazipfel an das Ligament mit einer Tantalumklammer fixiert Im ersten Fall wurde eine Naht nach Snellen (1869) gesetzt Im anderen *Fall ist bis jetzt kein Eingriff indiziert gewesen da wir keine Rezidiv*tendenz feststellen konnten Trotz Nahtinsuffiziens scheint die Sklera platte die Vorverschiebung der unteren Tarsuskante verhindern zu konnen Nach der Beobachtungszeit die zwischen 7 und 16 Monaten variiert sind samtliche Patienten beschwerdefrei und ohne Rezidive Auch das kosmetische Ergebnis ist zufriedenstellend

Ich mochte mit diesem kleinen Material vermeiden in Prozent zu rechnen und von Statistik zu sprechen Bei dem relativ schwer zu

Tabelle I
Entropium senilis recidivans palp inf Resultat nach Operation mit Sklera

	Frühere Operationen	Entropionop mit Sklera	Verlauf	Beobach tungszeit (Monate)	Lidstatus (April 73)
1 85 11 08 M W Re	Aug 71 v Blaskovics Sept 71 Kettesy	Nov 71	Nahtinsuff medial Juli 72 Snellen	16	*Normalstellung* doch leicht abgesunken
2 85 11 08 M W Li	Aug 71 v Blaskovics Sept 71 Kettesy	Dez 71	Unkompliziert	16	Normalstellung
3 99 08 26 E L Re	Sept 69 Snellen Mai 70 Kettesy Aug 71 v Blaskovics + Modifik Hallermann	Dez 71	Nahtinsuff lateral	16	Hängt nach unten durch Doch keine Rezidivtendenz
4 98 11 12 E R Re	Aug 69 Kettesy Febr 71 Kettesy Okt 71 v Blaskovics mit Modifikation	Aug 72	Unkompliziert	9	Normalstellung
5 93 02 26 F P Re	Mai 68 Snellen März 69 Kettesy	Okt 72	Unkompliziert	7	Normalstellung
6 93 02 26 F P Li	Mai 68 Snellen März 69 Kettesy	Okt 72	Unkompliziert	7	Normalstellung

behandelnden rezidivierenden Entropium scheint doch die Operation einen uberzeugenden Effekt zu haben weshalb die Methode fur diese Falle empfohlen werden kann

Schrifttum

Bangerter A (1969) Kleine Chirurgie der Lider *Ophthalmologica 158* 587—589
v Blaskovics L. (1922) Über die Ursache des senilen Entropiums *Klin Mbl Augenheilk 69* 136
v Blaskovics L. & Kettesy A (1970) *Eingriffe am Auge 4 Aufl S 49* Enke Stuttgart
Dalgleich R & Smith J L. S (1966) Mechanics and histology of senile entropion *Brit J Ophthal 50* 79—91
Duke Elder S (1952) *Textbook of Opthalmology* Vol *5 S 518?* Kimp on London
Fankhauser F (1966) Die Verwendung von konservierter Sklera in der Augen chirurgie *Albrecht v Graefes Arch klin exp Ophthal 170* 235—236
Hallermann W (1971) Misserfolge bei Lidoperationen und ihre Korrektur *Klin Mbl Augenheilk 158* 761—769
Johnson W A Henderson J W Parkhill E M & Grindlay J H (1962) Transplantation of homografts of sclera An experimental study *Amer J Ophthal 54* 1019—1030
Jones L T Reeh M J & Tsujimura J K. (1963) Senile entropion *Amer J* Ophthal 55 463—469
King jr J H Mc Tigue J W & Merryman H T (1962) Simple method of preservation of corneas for lamellar keratoplasty *Amer J Ophthal 53* 445—449
Lister A (1951) Malignant pigmented tumor in neighborhood of limbus treated by radical excision followed by corneoscleral graft Report of three cases *Trans Ophthal Soc U K 71* 97—110
Lohlein (1922) Eingriffe bei Entropium In *Graefe Saemisch Handbuch der Augenheilkunde 2/3* Aufl S *167* Springer Berlin
Paufique L. & Moreau P G (1953) La scléromalacie perforante Aspect histologique Traitment par greffe sclérale *Ann Oculist (Paris) 186* 1065—1076
Payrau P & Remky H (1961) Skleraplastik mit Sklerakonserven *Klin Mbl Augenheilk 138* 79?—804
Snellen H (1869) Intern Opth Kongr in Paris 1869 Zit bei W *Löhlein Eingriffe bei Entropium (s o)*

Anschrift des Verfa sers

Dr med E Wold
Ekorrgrand ?
Borås
Schweden

Discussion

T Waalen Do you use this method only by recidives of other ectropium operations?

Answer The method is meant for recidives All patients were operated on several times before as shown in Table I The method is technically easy and it does not take much time to perform it Sclera tissue is easy to get because same eyes are used in it as in corneal crafting

ACTA OPHTHALMOLOGICA
XXI MEETING OF NORDIC OPHTHALMOLOGISTS
Turku Finland 13–15 June 1973

Department of Ophthalmology (Head R Tornquist M D)
Region Hospital Örebro Sweden

SURGICAL REPAIR OF SCLERAL DEFECTS

BY

S STENKULA E KOCK M RYDBERG and R TÖRNQUIST

Summary

In ten patients we have used glycerine-preserved human scleras to repair large scleral defects Eight patients had scleral atrophy combined with old age or high myopia one patient had scleromalacia perforans and one patient had a scleral coloboma with uveal prolapse In seven cases the grafts were glued with Isobutyl-cyanoacrylate There were no complications

We have started transplanting scleras in rabbit eyes The experiments will be continued to study the tissue reaction and the survival of the grafts

Key words Scleral atrophy — scleromalacia perforans — scleral coloboma — scleral graft — tissue adhesive

Discussion

G *von Bahr* In closing a small scleral defect a piece of auricular cartilage can be used

Answer Sclera is always available after corneal transplantations The material is preserved in glycerine and ready for immediate use after rehydration It can be kept at room temperature for months

ACTA OPHTHALMOLOGICA
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*Ophthalmic Department E Rigshospitalet
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ELECTRO OCULOGRAPHY A CLINICAL NORMAL CASE SERIES

BY

ERIK KROGH

At present more exact measurements from the clinical electro-oculographic test are hampered by the extremely large interindividual as well as intraindividual variation of the various criteria (base value light peak dark through Arden quotient etc) Among the obvious reasons for this are the lack of a standardized technique and the indirect measurement of the corneo-retinal potential

A clinically normal case series totalling 142 eyes (72 patients) is presented and analysed The groups of female and male as well as right and left eyes were fully comparable No patients with medical or ophthalmological diseases or sex linked conditions were included

So far as the technical aspects are concerned the following must be emphasized The input impedance of the amplifier system is sufficiently large *e g* 50 megaohms The lower limit of frequency is zero so that a DC measurement is used The light stimulus is supramaximal

The Arden quotient is estimated using non parametrical statis tics The 50 %-percentiles show a significant sex difference and a significant decrease with age in both sexes The ordinarily accepted lower limit of the Arden quotient is clearly misleading in this case series and new values in accordance with the above mentioned results must be established

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Department of Ophthalmology (Head Professor G Karpe)
Karolinska Hospital Stockholm Sweden

WAVELET ERG DURING LIGHT- AND DARK-ADAPTATION

BY

L. WACHTMEISTER

The rapid oscillatory potentials (the so-called wavelet ERG) were studied in young and healthy subjects at different stages of adaptation to light as well as to dark The frequency and energy of the oscillatory potentials were calculated by a combined impulse and Fourier analysis

The oscillatory potentials of maximal energy and low frequency were recorded at the level of retinal sensitivity called the mesopic when the shift from photopic to scotopic vision or vice versa occurred This was observed during light adaptation to continuous background illumination during dark adaptation after light adaptation to continuous background or during light adaptation to short flashes of high intensity

(Full articles will be published in Acta Ophthalmologica)

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Steno Memorial Hospital Gentofte Denmark

PROGNOSTIC VALUE OF ERG (OSCILLATORY POTENTIAL) IN JUVENILE DIABETICS

BY

SVEND ERIK SIMONSEN

In the period 1964—66 a study was made of the ERG in juvenile diabetics with special reference to pathological change in its oscillatory component (O P) On the basis of investigation of 275 eyes from 141 juvenile diabetics there were three main findings

1) that the ERG might show significant changes even before ophthalmoscopically visible retinopathy was present

2) that re examination by ERG often showed a distinct change in the O P within 1—2 years

3) that ERG might be of prognostic value in diabetic retinopathy

Recently a follow up was done which included ophthalmoscopy and retinophotography on 114 of the 141 diabetics 6—8 years after the initial ERG examination The most important results of this study were

1) 36 eyes had changed from non proliferative to a proliferative state within the follow up period 31 of these eyes had initially shown significantly reduced O P (wavelet index) The remaining 5 eyes had had initially O P within the normal range 3 of them in women who had developed the proliferative retinopathy during pregnancy and delivery within the follow up period

2) Of the 58 non proliferative eyes with initially significantly reduced O P 31 developed proliferative retinopathy within the follow up period 13 were ophthalmoscopically unchanged (± 5 red spots compared with the initial retino photos) 14 had deteriorated ophthalmoscopically (over 5 additional red spots but no proliferations) several of them having clearly become preproliferative

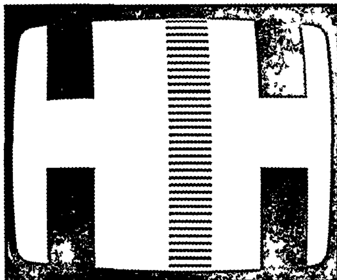


Fig 1
The double tooth pattern and a medium grade of the ribbon-like grating figure on the television screen In the actual test pattern the grating figure has the same brightness equivalence as the grey background

by thickness of the elementary black and white lines Each step of the grating figure can be made to appear and disappear at will without any change in the total illumination of the test area The background hue in the test area is particularly critical and an aspect of crucial importance inasmuch as the visibility of the grating ribbon is based on the big shape and not on the elementary lines if the background hue is too light or too dark

When measuring the visual acuity by this method that grating is looked for which when appearing suddenly in the middle of the test area can arrest the optokinetic nystagmus despite the continuing stimulus for the movement For each grating figure step a value of visual acuity is estimated experimentally The finest arresting step is not the same as that seen subjectively but is more coarse because of the rivalry between the evoking and arresting stimuli of eye movement

The beginning and end of the optokinetic nystagmus are recorded by an electric recorder for example an ERG apparatus in the same way as in used in other nystagmographic or oculographic examinations The appearing and disappearing of the grating and its grade of coarseness are recorded simultaneously thus obtaining the exact time relationships between the different stimuli and responses When examining small

children and other sensitive persons it is of course possible to observe the eye movement directly without any electrical contact leads This will however considerably impair the precision of the examination

The examination by this method must always be done with full refractive correction as all grating figures may create disturbing multiple patterns when looked at by an ametropic eye

Acknowledgement

This work has been supported by a grant from the Foundation Instrumentarium Tiedesaatiö Finland

References

Voipio H (1961) The objective measurement of visual acuity by arresting optokinetic nystagmus without change in illumination *Acta ophthal (Kbh)* Suppl 66

Voipio H & Hyvarinen L (1966) Objective measurement of visual acuity by arrestovisography *Arch Ophthal 75* 799—802

Voipio H & Lappi S (1969) Arrestovisography in strabismic amblyopia *Ophthalmologica 158* 320—325

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Discussion

M Warburg Which is the earliest age at which the method can be used? Which is the lowest I Q -level at which the method can be used?

Answer The youngest patients examined until now have been 5 years of age I believe however that also younger children (1/2—1 year) may be examined The problem is how to make them to concentrate on the test figure The same is valid when examining persons with a low intelligence quotient All disturbing environmental factors e g vertical lines on the walls have to be destroyed because they act as optomotor stimuli against the nystagmus

T Waalen Is it possible to observe the nystagmus by spectacle or is electronystagmografi obligatory?

Answer During examination procedure the eyes of the patient can also be observed directly

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Ophthalmic Department E (Heads J Edmund and E Gregersen)
Rigshospitalet Copenhagen Denmark

OPTIC AND DRUG PENALIZATION AND FAVOURING IN THE TREATMENT OF SQUINT AMBLYOPIA

BY

E GREGERSEN M PONTOPPIDAN and E RINDZIUNSKI

The authors report their experience of so-called penalization methods (optic and drug inhibition and favouring) in the treatment of squint amblyopia in a series of 23 children who had proved resistent to conventional occlusion therapy of a mean duration of 8 months (done with adhesive tape) The mean age of the patients was 5 years and the mean duration of squint 4 years before the institution of penalization therapy In most cases occlusion therapy had been abandoned by the patients themselves

In 17 of the 23 patients considerable visual gain was obtained by the penalization methods the mean visual acuity in the amblyopic eye increasing from 6/24 to > 6/9 Visual improvement was not obtained in patients in whom conventional occlusion therapy had been carried out correctly for a long time before being given up The penalization therapy lasted for an average of 10 months and was easy to carry out (only 3 patients giving it up)

(To be published in full in Acta Ophthalmologica)

Key words Squint amblyopia — optic and drug therapy — penalization methods — patients refusal of further occlusion

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CORNEAL REFLECTION OF A STRAIGHT LINE AND OPHTHALMOMETRY IN NORMAL PEOPLE AND IN ASYMPTOMATIC RELATIVES OF PATIENTS WITH KERATOCONUS

A preliminary report

BY

KÅRE HOLM

In 1937 Amsler reported that photokeratometry and ophthalmometry could be used to diagnose keratoconus at a stage when the condition was asymptomatic (keratoconus fruste) The first sign of keratoconus fruste would be a slight distortion of the reflections in the Javal—Schiøtz ophthalmometer together with an angulation of the horizontal line of the reflection of a right-angled cross

As one feature of the examination of 40 asymptomatic relatives of eight patients with keratoconus (from eight different families without any known predisposition to hereditary disorders) a photographic analysis of the corneal reflection of a right-angled cross was undertaken using a method which was an improvement upon Amsler s technique A corresponding examination was carried out on 40 normal persons of same age and sex distribution as the group of relatives

With the photographic method used an angulation of a straight line of 0 5 degrees can be demonstrated The maximal intraindividual variation is one degree (30 photographs of the same eye of three persons examined)

Among the sources of error which may influence the photokeratometry the following should be emphasized the patient does not fix well

the precorneal film varies in thickness pressure from the eyelids bad photographic focusing and variation of the thickness of the emulsion on the film

The examination showed that both in the group of relatives and in the control group there was an average angulation of the reflection of the single line of the cross amounting to 0 7 degrees (1 5 degrees as maximum) and no difference between the two groups could be demonstrated

The ophthalmometry showed that 10 persons in the group of asymptomatic relatives of patients with keratoconus and one person in the control group had bi-oblique astigmatism this being defined as astigmatism where the angular interval between the main meridians varies by $\geq$ 10 degrees from the right angle and the main meridians varies $\geq$ 10 degrees from the horizontal and vertical Bi oblique astigmatism may possibly be an abortive manifestation of keratoconus

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The Department of Ophthalmology (Head Docent R Tornquist M.D)
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A SIMPLE MODIFICATION OF THE TUDOR THOMAS EYE PIECE STAND

BY

M RYDBERG and E. WOLD

Some technical details of fixation of the donor eye for taking corneal grafts are discussed A modification of the Tudor Thomas eye piece stand to make it easier to fix the eye in a correct position is described

Key words Corneal grafting — corneal sutures — eye piece stand — fundus photography

The results of corneal grafting depend on many factors This paper is concerned with some details of taking the graft one way of placing the initial sutures and an aid to fixing the donor eye during these procedures

To avoid bevelled edges of the graft the trephine must be placed at right angles to the tangent of the apex of the cornea This presumes that most grafts are central The trephine must be maintained in this position during *trephination* To get the best possible match between the hole in the recipient cornea and the graft the IOP in the recipient eye and the donor eye should be as equal as possible

The shape of the cornea after grafting depends on the exact match between the graft and the recipient cornea As a rule four sutures are used to fasten the graft and the accuracy of placing these is very important Thereafter the other sutures single or running are inserted Dur-

ing these procedures the steady position of the donor eye or the graft is of significance

It is not unusual for textbooks to show the donor eye held in the surgeon s left hand while the right hand performs the trephination or the graft cutting Inevitably it is difficult to hold the eye in a correct position and to keep an even IOP at the same time Under these conditions the use of the Tudor Thomas eye piece stand is an help (Tudor Thomas 1935) The eye is then fixed and an eligible IOP obtained In the usual way the eye is stabilized by a suture through the optic nerve running in the central duct of the stand and the thread is fixed outside the stand Furthermore using this stand both of the surgeon s hands are free The sutures can be placed in the graft in many ways The graft may be placed on the recipient eye without any preplaced sutures or the sutures are placed with the graft held by different tweezers or holders Even if performed with the utmost care however there is a risk of damage to the endothelium With the donor eye in the stand trephination is done through only 2/3 of the cornea and then the sutures are preplaced in the graft During suturing the anterior chamber is maintained deep and the endothelium is protected As it is not necessary to hold the eye with the hand careful measuring is easy to get the sutures exactly placed Subsequently the cornea is perforated and the graft is cut with scissors

Even so the original Tudor Thomas stand has a disadvantage namely that since the duct for the optic nerve is central and quite vertical (Fig 1) but the optic nerve is off centre in relation to the posterior pole of the bulb it is impossible to get the axis of the eye vertical and the apex of the cornea will point at an oblique angle This makes it difficult to hold the trephine in exact position in relation to the cornea

To enable the operator to obtain an adequate position of the donor eye we have modified the stand The original channel has been filled up and a new oblique eccentric one drilled (Fig 2) As the optic nerve has been pulled down in the channel the desired position is easily obtained by rotating the eye

The distance between the centre of the optic nerve and the posterior pole is stated to be 3 mm It is difficult to find the correct distance of decentering the channel as the recess is conical To find the angle we have measured the distance between the centre of the optic disc and the fovea on fundus photos assuming that the fovea is equivalent to the posterior pole The West — Zeiss fundus camera (a measuring camera) has been used With the normal objective 1 mm on the photo corresponds to 1 20 of the fundus of the eye The average distance of 45 photos is

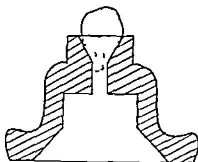


Fig 1
The original Tudor Thomas eye-piece stand

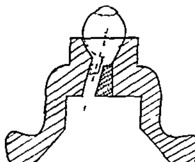


Fig 2
Modification of the Tudor Thoma
eye piece stand

12 mm which means 16° in the central fundus and consequently the oblique channel should be drilled at the same angle to the vertical axis through the stand

Reference

Tudor Thomas J W (1935) Technique of corneal transplantation *Trans ophthal Soc U K 55* 373

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Turku Finland 13–16 June 1973

University Eye Clinic (Head Professor H Forsius) Oulu Finland and Institute of Physiology Division of Medical Physics (Head Associate Professor K Kiviniutty) University of Oulu Finland

THERMOGRAPHY OF THE EYE DURING COLD STRESS

BY

P RYSÄ and J SARVARANTA

The temperature in the anterior parts of 20 eyes was measured with an infrared camera AGA model 680 Using a black body heat reference one can determine absolute temperatures with a precision of 0 1°C Comparing the anterior chamber depth measured optically and the rapid phase corneal temperature decrease in external temperature of —15 C a downward slope is obtained This correlation may possibly account for the commonness of some eye diseases in arctic districts

Key words Thermography — climate room — arctic eye diseases — anterior chamber depth — corneal thickness

The radiometric method for measuring the surface temperature of the cornea was used by Zeiss (1930) and Mapstone (1968)

Material and methods

In the present study the temperature in the anterior part of the eye was measured with an infrared camera AGA model 680 Using a black body heat reference one can determine absolute temperatures with a precision of 0 1 C In practice the first step is to align the camera against a radiant heat reference which consists of a thin copper plate whose outer surface is blackened with soot This plate functions as a wall of a container holding about 10 l filled with water which is maintained thermostatically at a constant temperature The isotherms of the

black heat reference and the object under study are then determined by the camera The absolute temperature of this object is obtained by adding the temperature difference between the two isotherms to the temperature of the heat reference The subject taking part in the experiment then sits on a stool and places his head in a stand so that it remains in a fixed position during the entire period of the measurements

The subject and the camera are placed in a room in which the temperature *can be adjusted from* +50 to —30 C *and the relative humidity from 0 to 80* °/₀ The size of the room is 3 × 4 × 2 5 m It is lit with a fluorescent lamp (giving little radiant heat) the wall are covered with black cloth to eliminate heat reflection and it is ventilated by fans placed near the ceiling in the corners A curtain is fixed so that any draught on the subject is kept to a minimum

The monitoring unit is placed in a room adjacent to the cold chamber The investigator and the subject can speak with one other by microphones placed in both rooms

Medical students were used as the subjects for there experiment At the outset the group consisted of 27 subjects of whom 7 were eliminated for various reasons (persistent blinking acute infections etc) A temperature of —15 C and a relative humidity of below 5 % were used in the cold chamber The temperature in the centre of each cornea was measured every minute for 10 minutes and every 5 minutes thereafter up to a total period of 45 minutes The right eye was

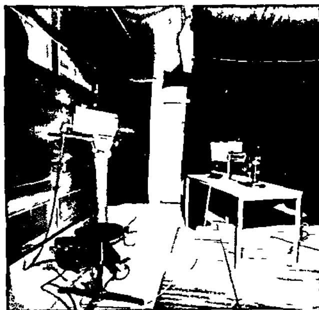


Fig 1

The infrared camera and the black body heat reference in the climate chamber

References

Mapstone R (1968) Measurement of corneal temperature Exp Eye Res 7 237—243

Zeiss E (1930) Über Warmestrahlungsmessungen an der lebenden menschlichen Hornhaut Arch Augenheilk 10 523

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Discussion

I Horven Did you find any difference in temperature between right and left eye?

Answer In the present study the results are given only in respect to the right eye By experience we know however that the temperature can change between the two eyes quite a lot

I Horven In the Eye Department Rikshospitalet Oslo I have measured the corneal temperature with a different methodological setup in cases with reduced ocular blood supply Eyes suffering from temporal arteritis may demonstrate a decrease in corneal temperature of several degrees centigrades values as low as +28 —29 C have been found Whether or not this technique will prove to be of value also in carotid occlusions is not yet evaluated although it seems possible

Answer The question is thoroughly discussed in the literature and the authors can send you a list of the literature if required

M Saari When the anterior chamber is deep the temperature goes down in cornea more slowly How do you explain this when thinking that the cornea lens and aqueous humour are avascular and in low anterior chamber the vasculature of the iris could nearer and possibly more rapidly regulate the temperature

Answer According to our hypothesis it is the thermal capacity of the aqueous i e the amount of the aqueous in the anterior chamber that rules the rapid temperature changes of the cornea When the anterior chamber is deep the amount of the aqueous is bigger too

M Saari Have you followed the rise in temperature of the cornea after you have kept it artificially cool?

Answer No Our equipment does not give us the opportunity for that yet

R Ralli Are you sure that you measured really corneal temperature? Not iris temperature?

Answer R Mapstone has shown in his work (1968) that the contribution of the emission of the aqueous (and the iris) to the emission of the cornea is so small that it can be ignored

Further he (among others) has calculated that the emissivity of the cornea (ε) lies between 0 97 and 1 *i e* near that of a black body radiator The precorneal film and the cornea have equal thermal behavior and they can be regarded as one continuous water phase

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Turku Finland 13–16 June 1973

Department of Ophthalmology (Head Professor Salme Vannas M D)
University of Helsinki Finland

HYDROPHILIC CONTACT LENSES — INDICATIONS AND FOLLOW UP

BY

MARTTI LIESMAA AND ANTTI VANNAS

Will be published elsewhere later on

ACTA OPHTHALMOLOGICA
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Turku Finland 13—16 June 1973

Department of Ophthalmology (Head Professor Salme Vannas M D)
University of Helsinki Finland

DRIVER S VISUAL ACUITY IN RELATION TO HIS DRIVING

BY

MARTTI LIESMAA

Will be published in the Transactions of the First Ergophthalmology Congress Madrid 1973

ACTA OPHTHALMOLOGICA
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Department of Ophthalmology (Head Professor Salme Vannas M D)
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Film program

TRABECULAR SURGERY OF OPEN ANGLE GLAUCOMA REMARKS ON MICROCIRCULATION

BY

S VANNAS P MÄNTYLÄ AND A VANNAS

Discussion

S Vannas This film had particularly a clinical aspect To pay attention to the pathological microcirculation of the different forms of the open-angle glaucomas and further to show how to avoid bleedings by using preoperative FAG illustrations as a guide

The results of our trabecular surgery are to be published later Trabeculotomy seems to be suitable for simple glaucoma (as well as trabeculectomy) From operative complications leading to failure the occasional bleedings might be rather important even in simple glaucoma but the more so in capsular and neovascular glaucoma Hence we now prefer trabeculectomy with peripheral iridectomy In the preoperative FAG of the iris and the perilimbus the site of trabeculectomy can be selected and during the operation if necessary the casual bleedings may be stopped by cautery under the water irrigation Like this good results were achieved even in neovascular glaucoma where the danger of bleedings and postoperative anterior synechiae is biggest As to sinusotomy we don t have any experience

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Department of Ophthalmology (Head Professor Salme Vannas M D)
University of Helsinki Finland

Film program

COMBINED IRIDOCYCLECTOMY AND TRABECULECTOMY WITH SCLERECTOMY FOR TENSION RAISING TUMOUR OF ANTERIOR UVEA

BY

S VANNAS C RAITTA AND P MÄNTYLÄ

GENERAL MEETING

Gunnar von Bahr

Report on Nordisk Oftalmologisk Litteratur Ring (N O L R)

The accounts were submitted The activities will continue as hitherto but the membership dues have to be increased to 30 Sw Crowns a year

Congressus XXII ophthalmicorum septentrionalium

The Swedish Ophthalmologic Society invited to the next Nordic Meeting in Sweden in 1975

The question of languages at the Nordic Meetings was discussed The majority of those present had the opinion that the traditional praxis that Nordic languages should be used should be followed It should be considered if there should be simultaneous translation Finnish-Swedish It was also recommended to publish abstracts of the papers in advance

Nordic courses in Ophthalmology

The ophthalmological societies were asked to arrange Nordic refresher courses for eye specialists

Agenda for the General Meeting should be published in advance

Poul Brændstrup

Report on Acta Ophthalmologica

The Scandinavian ophthalmological societies are the owners of Acta Ophthalmologica Our periodical has been issued continuously since 1923 meaning an existence throughout half a century

Since the last report in Reykjavik 1971 the Acta has shown a steady progress Volume 49 1971 and volume 50 1972 comprised 983 and 904 pages respectively During these two years eight supplementa were issued

30 per cent of our subscribers live in Scandinavia and 70 per cent outside our area — all over the world which is an encouraging fact So Acta Ophthalmologica now appears not only as a local but as an international periodical Let us be happy for our Acta Ophthalmologica

Presentation of the K K K Lundsgaard Medal

This medal should be awarded the author of the best paper in Acta Ophthalmologica in the volumes 49 and 50 The committee in charge elected »Vital Staining of Cornea and Conjunctiva Supplementum 113 1972 written by M S Norn M D

Professor Brændstrup presented the K K K Lundsgaard Medal in gold to M S Norn who for years has contributed and still contributes superior and extensive pioneer work in the field of ocular vital staining



M S Norn M D

MEMBERS OF THE MEETING

Austria

Hochmayr Walpurga

Denmark

Barfoed Poul
Bay Michael
Bruntse Else
Braendstrup Poul
Christensen Sigbrit
Damgaard-Jensen Ehlert
Dreisler Knud
Edmund Jens
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Sweden

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Boström-Smith Inga Lisa
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Esklund Alf
Gjotterberg Magnus
Hallen Barbro
Haptén Klas
Hedbeck Krister
Hedensiö Bertil
Hedvall Inger
Huelo Ants
Hjortzberg-Nordlund Ulla
Holm Klas Krister
Jahnberg Peder
Jansson Folke
Jerndal Tord
Karpe Gösta
Kassman Ture
Klingberg Stig
Kronning Eric
Lehmann Birgitta
Linner Erik
Ljungstrom Stig
Lunt Tönis
Moulun Elisabeth
Nilsson Sven Erik
Norrby Åke
Nylander Ulf
Olsson Gunvor
Pallin Per
Palm Erik
Permalm Hugo
Philipson Bo
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Wahlberg Ivar
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Widakowich *Johannes*
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ACTA OPHTHALMOLOGICA
SUPPLEMENTUM 124

GENETICS AND PHYSIOLOGY OF COLOUR VISION

II

by
GEORG H M WAALER
(From the institute of forensic medicine University Oslo)

MUNKSGAARD
COPENHAGEN 1974

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Index

	Page
Introduction ('The colour vision region' and 'The nine equations')	5
Part I The pigments in the cones and rods	7
Part II The many *different hereditary properties in* colour vision	18
Part III Protan-deutan crossing-over	25
Summary	35

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INTRODUCTION

('The colour vision region and 'The nine equations')

The picture of human colour vision has developed into a very complicated multitude of properties, not only as regards colour blindness and so-called defective colour vision but also normal colour vision

Regarding colour blindness, there has been known for a long time that there are six types deuteranomaly (in the literature designated DA or Dl (Waaler 1927) extreme deuteranomaly (EDA) deuteranopia (D or Dp) protanomaly (PA or Pl) extreme protanomaly (EPA) and protanopia (P or Pp) The first three are together called deutan whereas the three last mentioned are summarized as 'protan It was postulated (Waaler 1927) that these properties derived from four (six) particular genes in the X chromosome as demonstrated through investigations of colour blind sons of conductor mothers When females analysed through male family members were shown to have the gene for deuteranomaly in one of their X chromosomes and the gene for deuteranopia in the other it turned out that the first dominated over the second In the same way Pl dominated over Pp with the extreme anomalies as intermediate stages both as to the deviation from normality and as to dominance Females analysed to have a protan gene in one X-chromosome and a deutan gene in the other were found to have normal colour vision Although the last fact had the most natural explanation in the assumption of there being two different loci for the deutan family and the protan family (within each family the genes were supposed to be alleles) the author developed his one locus theory as demonstrated in an earlier paper (Waaler 1927) This hypothesis was (Waaler 1967) developed into an one-cistron hypothesis and the author's picture of the one locus hypothesis was shown to have been a foresight of the modern cistron conception

Also individuals with normal colour vision have distinctly different properties Thus there are males with their point of pure green on the spectrum (not blue green or yellow green) at the average of 515 nm and other males with this point at 525 nm (Rubin 1961 Richards 1967 Waaler 1967) The genes, as well as the

properties among males were called G_1 and G_2 respectively Among females there were three genotypes G_1/G_1 G_1/G_2 and G_2G_2 and also three phenotypes G_{11} G_1 and G_{22} as the heterozygotes could be diagnosed on the basis of intermediate reactions

In the same way there are also two different points on the spectrum where males with normal colour vision have the perception of pure blue (not blue green and not lilac) at 487 and 479 nm (Waaler 1968) Here the designations B_1 and B_2 were used The genetics and the finding by females were corresponding to that described for the G properties The manner of heredity, hinted at above was confirmed through investigations on parents and children (Waaler 1967 1968) The G and B properties were independent of each other there being four types of normal colour vision among males G_1B_1 G_1B $G B_1$ and G_2B_2

The G genes were supposed to be localized at two different places (mutons) in the same cistron This was a transformation from the old (1927) one locus hypo thesis to the one-cistron two muton hypothesis

The B genes were supposed to be localised in an other neighbouring cistron It was said that future investigations would decide if B_1 and B_2 were real alleles or if they also were placed as two different mutons in this cistron (Waaler 1973b) The results of these investigations are found in Part II of this essay and they show that B_1 and B_2 are localized at two different places (mutons) in the same cistron That is the facts should be as earlier postulated for the G genes

The real alleles to G_1 G_2 B_1 and B_2 which could be called g_1 g b_1 and b were supposed to be unable to produce any reaction in retina However during the seldom occurring event of crossing-over (for instance with two female X-chromosomes G_1g_2 and g_1G_2) (see Part II and Part III) one would expect to find the fol lowing new patterns in the X-chromosome $G_1G_{\circ}$ $g_1g_{_}$ B_1B and b_1b The pro perty of $G_1G_{_}$ males were called G_m (m from Greek mesos intermediate between 1 and 2) (Waaler 1973a) We would also expect to find a property which could be called B_m

In the following Part I the constellation $g_1g_{_}$ (that is when the genes are not in competition with the capital letters') is tentatively supposed to produce the same property as G_1G_2 but possibly at a slower speed and perhaps in a smaller quanti ty But the important fact remains that there exists a balanced quantity (this idea is changed in Part II) of both properties g_1 and $g_{\circ}$ For the constellation $b_1b_{_}$ the same reasoning can be applied

As regards colour blindness it was postulated that there in a third cistron either adjoining or neighbouring were four quantitative allelic genes n l e and p which combined with G_1 would give the protan family whereas the combination with $G_{_}$ would give the deutan family (These thoughts will be modified in Parts I and II) Thus the discussion in the literature of the deutan protan problem i e

the colour vision for the deutan/protan females and the possibility of protan deutan crossing-over (see Part III) concerns the G_1 and G_2 genes

The fixation of an observer's point of pure green is not easy as the point cannot be determined exactly Therefore the author has developed a method of nine equations which seems to give a better and safer division into two groups, and also gives a more assured diagnosis of the G_1/G_2 females. This has also been profit able for the discovery and description of some new types of normal and defect colour vision (see Part II)

The fifth of these nine equations (see Waaler 1967) is the usual Rayleigh equ ation where the yellow light in the lower semicircle of a Nagel s anomaloscope has the wavelength 589 nm and the mixing red and green in the upper semi-circle have the wavelength of 670 and 546 nm respectively In model II of this anomaloscope it is possible to change the spectral locus of the yellow light over the complete spectrum from purple to violet the two other colours being at the same time par allel shifted On four points on each side of the usual Rayleigh equation point, with the lower semi-circle lightened from a green yellow colour (574 nm) to an orange colour (603 nm) it will be possible to find the eight other equations (On model II there are three screws a brightness screw influencing the intensity of the light in the lower semi circle a mixing screw giving different relative amounts of red and green in the upper semi-circle and a so-called main screw which enables the move ment of the coloured light over the whole spectrum)

Referring to Table 1 (from my 1967 paper) we will especially notice the figures for the G_{12} females They are as averages placed near the G_1 values for the males in the green part of the nine equations and near G_2 values for the red part passing through the ordinary fifth point with fluctuating values occurring there This fluctuation in the usual Rayleigh equation is repeatedly found in other types (important here in Part II and III)

Table 1 Nine equations on the scale for the main screw from 260 to 240 Average values on the scale for the red green mixing screw

The main screw at	260	257	255	253	250	247	245	243	240
The brightness screw at	17	18	18	17	16	15	14	12	7
Averages for G_1 males	13.3	18.3	23.2	28.1	38.0	47.8	53.4	59.9	65.5
Averages for G_2 males	15.8	20.8	25.8	30.8	40.9	50.6	56.7	62.0	67.1
Averages for G_{12} females	13.9	19.0	23.7	29.0	38.9	49.7	56.1	61.4	66.7

PART I

THE PIGMENTS IN THE CONES AND RODS

Earlier (Waaler 1967 1968 1969 1973a and b) I have written upon the heredity of the G and B properties

As shortly mentioned in the Introduction the G properties are found in two

groups of males with two different points of pure green, whereas the B properties are found in two groups of males with two different points on the spectrum where they perceive pure blue

Points of pure yellow and red (Waaler 1968) can also be made out. From an individual s blue point to his yellow point he has a perception of green that is a hint of green near the blue point to a hint of green near the yellow point, greatest perception of green occurs in the middle (not necessarily at or near the green point but in fact independent of this point) A curve describing this green perception is called a green valence curve In the same way, a yellow valence curve exists between an individual s green point and his red point, a maximum occurring independent of the point of pure yellow

These two valence curves were compared (Waaler 1969) with the absorption curves of the cyanolabe, chlorolabe and erythrolabe cones (Rushton 1958 1962 Marks 1963 Marks et al 1964) The green valence curve corresponds to the chlorolabe absorption curve The yellow valence curve corresponds to the erythrolabe absorption curve The maximum of this curve lies at 577 nm where there is no sensation of red The erythrolabe cone was therefore renamed the chololabe cone (Waaler 1969)

The cyanolabe absorption curve, with a maximum at 447 nm, and its hypothetical porphyrolabe (deep octave) part with a maximum in the infrared (894 nm) (Waaler 1969) crosses the valence curves at the points of the pure colours i e crossing the green valence curve at the blue points and there balancing counteracting and cancelling the green (pure blue is thus the result) It also crosses the yellow valence curve at the green points, thus balancing and cancelling the yellow (pure green) In addition the porphyrolabe part (see Fig 1 from Waaler 1969) crosses the yellow valence curve at the red point, and the green valence curve at the yellow point, producing the observer s feeling of colour pureness at both these points (For details of this reasoning see the pages 51 and 52 in Waaler 1973b)

The points of pure blue are thus the product of the green valence curves (two different for B_1 and B_2 individuals) and these curves are the effect of the light energy absorption in the pigments of the chlorolabe cones These two different pigments are thus the real hereditary properties produced by the B genes In a corresponding way we have the three steps the green points the yellow valence curves and the pigments in the chololabe (erythrolabe) cones produced by the G genes. Later in this Part I we shall take a step further backwards, i.e nearer DNA, to the isomerases as the 'real hereditary property

The pigments in the cyanolabe cones and the visual purple in the rods are of course also produced from DNA. But until now there are no signs of there being more than one of each, that is all individuals have only one visual purple (see some remarks further in Part II) and only one pigment specific for the cyanolabe

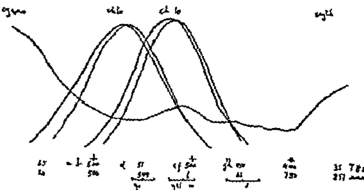


Fig 1 Proposed picture of the absorption spectra from the chlorolabe (B_1 and B_2) the chololabe (G_1 and G_2) and the cyano labe cones of males with normal colour vision

cones Thus it might be usual not to think of such properties as being hereditary but of course these unique pigments are in fact also hereditary as they are de rived from DNA as hinted above

We must therefore look for six different pigments one for the rods (here we have the visual purple) two for the chlorolabe cones two for the chololabe cones and one for the cyanolabe cones For the last mentioned though we might pos sibly have two different pigments one reacting in the violet region of the spect *rum and one reacting in the purple (the porphyrolabe deep octave') part* (see Waaler 1969 and especially pages 66–67 1973b) We thus should perhaps have *to search seven different pigments*

The basis for this search for pigments we find in the multitude of important *investigations made on these substances* primarily *by George Wald (1959)*

Wald (1935a) was the first to remark on the connection between vitamin A deficiency and night blindness *He found* vitamin A in the tissues of the eye and particularly in the region of the pigment epithelium tissue Vitamin A is trans ported from the blood of the choroid through this pigment epithelium tissue into the rods and cones The CH_2OH group is then oxidized to a CHO group in a carotenoid which Wald (1935b) called retinene All available evidence permits the assumption that visual purple is a conjugated protein in which the retinene is the prosthetic group Under the effect of light energy absorption by visual purple (leading to bleaching of the pigment) the physiological effect is practically momentary and reaches the visual center in the brain in 50 msec (see Waaler 1973b) whereas the chemical reaction, the loosening of the retinene from the protein is a comparatively slower occurrence and is the last link in a chain of reactions

(Concerning the figure of 50 msec I would like to clear up the following points In the paper (1973b) I have described the events in the receptors the nerve cells and the axons as a flow of Na^+ from the retina to the visual cortex Such a flow would however not travel from the retina to the cortex in such a short time as 50

msec What really happens is that a wave of depolarization occurs (a smaller potential difference between the outside and inside of ganglion cells and their axons) But this electric current would on the other hand not use such a long time as 50 msec What produces this time lag (measured in electroencephalography) is the passage of Na^+ over the synapses 1) from receptor to bipolar cells 2) from bipolar to ganglion cells 3) from their axons to the ganglion cells in the lateral geniculate nucleus and probably also 4) from the last mentioned axons to the nerve cells in the visual cortex The total time of all these events including the real electric current will be around 50 msec)

Wald (1936) found a cycle Light energy splits visual purple to retinene in the all trans form and protein then we get vitamin A and protein (the equilibrium for vitamin A and retinene in tissues is placed mainly towards the side of the vitamin) and then the transformation back again to visual purple in the dark. The *loosening of retinene the bleaching is a first order reaction whereas the regeneration* of visual purple is a second order reaction The synthesis requires an isomerisation as the all trans form of retinene cannot be used directly for the regeneration of visual purple

Wald (1937) called the *protein opsin* Wald et al (1955) gave the *special name* scotopsin for the opsin used in building the visual purple this giving the absorption curve in darkness whereas a photopsin is supposed to be responsible for the light absorption in daylight (when we see colours) The scotopic maximum was found to lie near to 500 nm whereas that of the photopic occurred around 550 nm

Wald et al (1955) also found that a specific retinene termed neoretinene b, when added to scotopsin gave rhodopsin with absorption maximum at 500 nm Another retinene isoretinene a added to scotopsin gave an iso-rhodopsin with a resorption maximum occurring at 487 nm (difference 13 nm)

Wald (1959) described the mentioned cycle in which alcohol dehydrogenase and DPN are included The synthesis of rhodopsin from opsin and retinene requires free -SH groups on the surface of the opsin and the bleaching sets free two or three -SH groups per molecule Wald stated that one quantum of light (photon) is absorbed by one molecule of the visual purple This is the photochemical law of Einstein one quantum per molecule If a photon is not absorbed there will be no physiological or chemical effect. The light absorbing electrons are localized at the boundary between the protein and the chromophoric group (the retinene) The effect of the photon absorption is that an acid binding group and the just mentioned -SH groups are set free

In the literature it has been discussed whether the binding between retinene and opsin is a carbon nitrogen or a carbon sulphydryl bond Dartnall (1957) has proposed that both bonds are used at several points

Rushton (1957) showed that the isomerisation of the all trans form is condi

tional upon a water soluble factor an isomerase which can be extracted from the retina

We now have the basis for our search for the six or seven different retinenes. A retinene contains a hexagon and a side chain with conjugated double bonds ending in the aldehyde goup (with a double bond between C and O)

The hexagon exists as two types (see Figs 2 and 3) that is, with a double bond occurring between C_1 and C_6 (type 1) or a double bond occurring between C_5 and C_6 (type 2) The all trans forms of these two types are found in equilib rium in the tissues Furthermore we have a retinene_ derived from vitamin A_2 with an additional double bond occurring between C_3 and C_4 The above men tioned retinene derived from vitamin A_1 may then be called $retinene_1$

In addition to the all trans form we have the 9 cis the 11 cis, the 13-cis and the 9 13 dicis isomers (see Figs 4 5 6 7 and 8) From investigations of many species of fish there seems to be (Bridges 1965) a unique series of discrete op sins which combine with $retinene_1$ and retinene_ chromophores to yield two visual pigment series (Also Dartnall and Lythgoe (1964)) After Bridges (page 232) It may be shown empirically that the central wavelength of a pigment group is given approximately by the linear equation

$$\lambda = nx + 462$$

where n is an integer giving the series number of the opsin and x is the λ max shift per unit change of opsin the best figures being 6 3 for the vitamin A_1 series and 10 1 for the vitamin A_2 series

Vitamin A_2 is charaecteristic for fresh water fishes whereas A_1 is characteri stic for marine and land vertebrates As retinene_ is not found in man this re tinene will not be further discussed here

(Wald (1957) has found that fishes moving from fresh water to sea water or in brackish water may have both types A fish moving down stream have already produced the marine type and upstream migrants already possess the fresh water type The facts found by Bridges and Wald are interesting in relation to the thoughts published by Monod (1970) according to which fishes throughout thousands and millions of years have tried the different pigments produced through occasional and seldom mutations and have kept a pigment as their pro- perty it being the most convenient for them in their usual surroundings for example in deep water with its degree of light. I have mentioned the same thoughts (1973b) for the specific visual pigments in the cat s eye which is a noc turnal animal and supposed to be colour blind)

If we try the four integers 10 11 18 and 19 in the above quoted equation we find that the λ max should lie at 525 0 531 3 575 4 and 581 7 It is interesting to compare these four figures with some figures from my earlier works (1968 and 1973b) The maxima for the green valence curve for B_o individuals (526) and

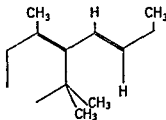


Fig 2 Hexagon type I
(NB! Error a missing side in the hexagon)

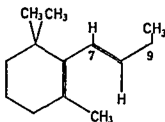


Fig 3 Hexagon type 2

B_1 individuals (531) and the maxima for the yellow valence curves for G_1 individuals (574) and G_2 individuals (580)

I have not really measured these maximum points on the valence curves I have only thought, that they are placed in the middle between the pure colours

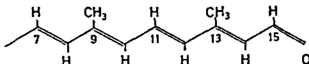


Fig 4 The all trans form of the retinene

calculated as terahertz (THz) These points are difficult to ascertain especially for the yellow valence curves the red point and the point of pure green. Furthermore the height of the crossing with the cyanolabe curve (see Fig 1) (these crossing points are the places for the pure colours') will influence the

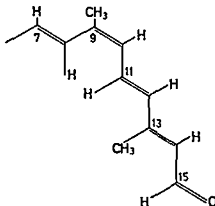


Fig 5 The 9-cis form of the retinene

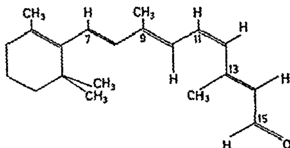


Fig 6 The 11-cis form of the retinene

position of the curve maximum In addition we must remark on the fact that the figure 6 3 according to Bridges is supposed to be only approximately calculated All the same however the above mentioned comparison between the two rows

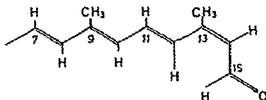


Fig 7 The 13 cis form of the retinene

of four wavelengths indicates that the figure of 6 3 nm also has something to do with the characteristics of the human pigments

Concerning the figure of 6 3 nm I would like to remark that in dealing here with light energy transition it is more natural to use the frequency measurement

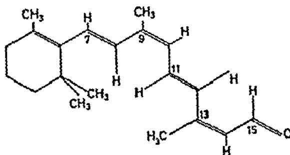


Fig 8 The 9,13-dicis form of the retinene
(NB' Error The hexagon should be of type 2)

(THz) which will be linearly connected to the energy of one photon. The wave length *measurement will possibly not show this linear connection over the whole* spectrum I have found that it should be more natural to use the figure of 5.3 THz from 671 THz (447 nm the cyanolabe maximum) in the following formula

$$671 \text{ THz} - 5.3 \cdot x$$

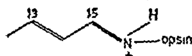
When we here for x use 19 20 28 and 29 we get the following

570.3 565.0 522.6 and 517.3 THz

When we translate these figures back again to wavelength measurements we get 525.88 530.97 574.05 and 579.93 These figures in fact equal my old postulated maxima for the valence curves these being *526 531 574* and *580* nm The figure of 5.3 THz is obviously selected to satisfy this conformity

When the vitamin A having passed the pigment epithelium tissue arrives at the rods and cones the two above indicated types of all trans retinene are prod*uced after simultaneous oxidation and isomerisation to form the different* cis isomeres These are then linked to the opsin The bonds between retinene and opsin are ionic and occur 1) between C_{15} (CHO) in retinene and an N in opsin and 2) between an S in the opsin and a C in retinene adjoining one of the double *bonds in retinene. Thus, there is a specific correlation between the specific iso*merases and the distance and placement of the SH and NH_2 groups on the sur face of the opsin

As to the carbon nitrogen bond at the aldehyde end of retinene investigations by Akhtar and Wilson (1971) have shown *for visual purple (in bovine retina)* that the nitrogen is the ε amino group of lysine Probably we can assume that the corresponding group in arginine could play the same role Akhtar and Wil son have formulated the Schiff s base with the C_{15} in retinene in this way Fig 9



that is a protonated retinylidene

The proton will have a tendency to shift the conjugated double bonds resulting in a positive charge at C_{13} C_{11} C_9 C_7 and C_1 or C_5 in the hexagon In Fig 7 we see that there is a small degree of steric hindrance due to the two hydrogen atoms where the coplanarity still is kept by changing the angles at C_{13} and C_{14} *If a* cysteine *exists on the surface of the opsin near some of these carbon atoms* we may get an ionic not covalent bond here Thus the double bond will be weakened thus making the attraction of the SH group stronger We discover here the important connection between the isomerase and the constitution on the sur *face of the opsin Where there is a suitable distance between lysine (or arginine)* and cysteine the specific isomerase will get into function and produce the 13-cis isomere bound at these two points.Also at C_1 or C_5(the two types of the hexagon)

such an ionic bond occurs between S and the partly protonated C Thus we have a specific arrangement distance and direction on the surface of the opsin Cysteine – cysteine – lysine which is intimately connected with a specific 13-cis isomerase

From Fig 6 it appears that there is a steric hindrance at the 11-cis retinene due to the neighbourhood of CH_3 to H as explained by Pauling (1945) The retinene is therefore brought out of coplanarity and is linked to opsin (as it is supposed to be by visual purple in the rods) in an energy rich stressed position This is regarded to be the cause of the broad distribution of the absorption curve, over the whole visible spectrum as distinct from the three absorption curves for the cones over a narrower and selected region of the spectrum From Fig 3 it is evident that the double bond C_5 C_6 due to the same steric hindrance cannot be coplanar with the conjugated double bonds in the side chain. But the type 1 (Fig 2) may show coplanarity from C_1 C_5 to C_{15}

The other forms of retinene 13-cis 9-cis and 9 13 dicis retinene and possibly the all trans form can therefore be used as explanations for the pigments other than the visual purple The difference between types 1 and 2 of the hexagon (Figs 2 and 3) may explain the b modality of the green and yellow valence curves The difference between the retinene with type 1 and 2 may correspond to the mysterious figure 6 3 as it is reasonable to assume that type 1 will correspond to a maximum of absorption at about 6 3 nm longer wavelengths, that is at a point where the photons have lesser energy

I shall here assume that the 13-cis isomer forms the basis for the yellow valence pigment and the 9-cis isomer for the green valence pigment. Both these cis forms are supposed to give two different but closely related pigments with their points of maximum absorption occurring at around 6 3 nm between the points dependent on the two forms of the hexagon type 1 and type 2 (Figs 2 and 3) The optimal direction of the retinene is vertical to the axis of the receptor and we can see in Fig 5 that the 9 cis form already has a tendency to point downwards on the side of the surface of the opsin It is for this reason that I have selected the 9-cis form as belonging to the green valence This is because through reinforcement of this tendency we could have an explanation for the circumstances which may give rise to the different degrees of deficiency in green and red perception

I have here inserted a very important quotation from Granit (1947) The carrier weight of a chromoprotein is the weight of that part of the molecule which contains one chromophoric group It was found (for visual purple) to be about 26 500 The protein is also bound to phospholipines The weight of the phospholipine and the mol wt for retinene (288) may explain the difference between the figure of 26 500 and Svedberg s fundamental protein unit of 17 600 Svedberg found that the mol wt. of other chromoproteins are also in the order of 26 500

The mol wt of opsin was found to be 270 000 and thus every molecule of opsin carries ten chromophoric groups

The ten chromophore groups occur on the surface of the opsin molecules A twisting of these molecules could move the retinenes away from the above mentioned optimal direction and thus explain the different reductions of the green valence curves in colour vision defects Yet this idea will not be further discussed here

I accept of course that the 11 cis isomer forms the basis for the visual purple in the rods The question as to whether two forms exist (with the two types of the hexagon) is a reasonable one Could the two maxima be $5 \times 6.3 + 462 = 493.5$ and $6 \times 6.3 + 462 = 499.8$? With respectively 20 per cent and 80 per cent of the two substances we would get an apparent maximum (on a really bimodal distribution curve) at 498 nm which is the figure given in the literature for the scotopic maximum and which is dependent on the rod pigment Some pages above I mentioned the two figures from Wald et al (1955) that is the maximum for rhodopsin occurring at 500 and that for iso-rhodopsin at 487 nm Could these two pigments correspond to 499 8 and (2×6.3 less) 487 2? With 14 per cent of the substance at the shorter wavelength we would again get approximately 498 nm as being the apparent maximum of the possibly bimodal curve

I do not know with what certainty this broad region of maximum can be ascertained or how certainly one can deny that there is a real bimodality So in this instances I can neither postulate nor deny that there are two types of visual purple in the rods

The 9 13 dicis isomer is supposed to be the basis for the pigment in the cyanolabe cones in the violet region whereas the all trans form as a hypothesis is supposed to be the basis for the porphyrolabe part of the complicated cyanolabe curve in Fig 1 I have already (1973b) indicated that the two isomers are linked to the opsins in the cones in small quantities whereas most of it exists as free all trans form in the fluid The all trans form is of the two types 1 and 2 (with respectively 6 and 5 conjugated double bonds (including the aldehyde and later the imine bond) When the rods are stimulated by high energy light (blue and violet) I indicated that type 2 will be transformed to the 9 13-dicis isomer and the linkage to the opsin will increase This will lead to what we might call the cyanolabe effect with absorption maximum occurring at around 447 nm However if the rods were stimulated by low energy light (red deep red and purple) I indicated further that the all trans form would continue to exist and an increasing quantity of type 1 would be fixed to the opsin This conjugated protein was suggested to have an absorption maximum around 894 nm (in the infrared) (see Fig 1)

To recapitulate the cyanolabe pigment is built up from 9 13-dicis retinene and an opsin which have three cysteine acids lying at a proper distance and direc

tion to point towards C_{13} C_9 and C_5 whereas a lysine or arginine will point towards C_{15}

We shall now make a survey of the different chromoproteins

There is a general rule that the greater number of conjugated double bonds present, the lower the energy which is needed to be absorbed by the pigments for procurement of their physiological effect

Firstly we will discuss the 13-cis retinene which has the type 1 hexagon There are *four conjugated double bonds to the left (on Fig 7) of C_{13} and two (with the* imine) to the right or one double bond to the right of C_{14} This corresponds to an absorption maximum at 580 nm i e one of the yellow valence curves With type 2 of the hexagon there are three conjugated double bonds to the left of C_{13} and two (or as above one) to the right This corresponds to the absorption maximum at 574 nm i e the other yellow valence curve

Secondly we can study the 9 cis retinene which has the type 1 hexagon There are two double bonds to the left of C_9 and four (or three as above) to the right. This is concerned with the absorption maximum at 531 nm i e one of the green valence curves With type 2 hexagon there is one double bond (if we observe the conjugated double bonds only) to the left and four (or three as above) to the right, and this corresponds to the absorption maximum at 526 nm i e the other green valence curve

The sum of the double bonds is the same for both these retinenes as is shown in Table 2 This seems for me to indicate that the bonds near the hexagon that is in the neighbourhood of the sulphydryl links, are more important for the establishment of the absorption maximum than the double bonds in the direction of the imine

	Number of double bonds			
	Near sulphydryl	Near imine	Sum	Wavelengths at the abs max.
Cis 13	4	2 or 1	6 (5)	580 nm
	3	2 or 1	5 (4)	574 nm
Cis-9	2	4 or 3	6 (5)	531 nm
	1	4 or 3	5 (4)	526 nm

Table 2 Number of conjugated double bonds and wavelengths at the maximum of light absorption

It is not necessary to say more about the rod pigment the visual purple and the 11 cis retinene bound to a nitrogen in lysine and to two sulphydryl groups because this is quite a unique type having the scotopic absorption curve as the result

of the photon absorption Remarkably the 11 cis and 9 13 dicis have their hexagons and their C_{15} occurring at the same distance and mutual direction as seen in Figs 6 and 8

The 9 13-dicis retinene with type 2 hexagon has two double bonds to the right of C_{13} C_9 and C_5 *or one double bond to the right of* C_{14} C_{10} and C_6 This constellation requires the highest energy to give the absorption maximum at 447 nm

It must be up to the chemists the biochemists or physical chemists to judge the probability of there existing a correlation between the above described different numbers of double bonds and the maximum absorption points

The all trans retinene (type 1 hexagon) which is supposed to have an absorp*tion maximum at 894 nm in the infrared when linked to the opsin* has six double bonds from the imine to C_1 I am not certain whether the physical chemists after making their judgment will find a connection which could support my old deep octave hypothesis (447 as opposed to 894 nm) However if the idea of the all trans form of retinene being the basis for the porphyrolabe pigment is correct then the old deep octave hypothesis becomes superfluous Then the absorption maximum could lie higher and have more of its left shoulder inside the visual spectrum which seems to me more reasonable than the form height and position we find in Fig 1

The conclusive idea is that the gene G_1 produces a 13-cis isomerase which selects the hexagon type 2 of the all trans retinene whereas the 13-cis isomerase from G_2 selects type 1

In the same way the 9-cis isomerases produced by the B_1 and B_2 genes select hexagon type 1 and 2 respectively

The G genes are thus the basis for the yellow valence curves Thus they are the basis for and derive their names from the two G properties

In the same way the B genes are the basis for the two green valence curves and thus are the basis for and have their names from the two B properties

It is interesting to observe that the first product from these genes in DNA (the isomerases) are enzymes as is often (always?) the case in genetics

PART II

THE MANY DIFFERENT HEREDITARY PROPERTIES OF COLOUR VISION

As demonstrated in the Introduction there are a great number of variations regarding normal colour vision and colour blindness properties In this Part II we assume that the colour vision region in the X-chromosome contains three cistrons one for the G properties with four different types G_1 G_1G_2 (or G_m) g_1g (or g_m) and $G_$ and one cistron for the B properties with the four types B_1 B_1B_2 (or

B_m) b_1b_- (or b_m) and B_2 The existence of the types g_m and b_m shall be discussed further in this Part II The third cistron has five quantitative alleles n r_1 r_2 r_3 and r_4 (*r meaning reduction of the green valence*) (*not four alleles* as described in Waaler (1973b) n 1 e and p) Thus in all we should then have 4 × 4 × 5 = 80 possible combinations in the colour vision region The females may then have $\frac{80 \cdot 81}{2}$ = 3240 different genotypes However it is not necessary to make it so complicated We could say that we have 4 × 4 = 16 normal types (perhaps only 3 (G types) × 3 (B types) = 9) In the case of colour blindness the B genes are of no (or very little) influence here Therefore we will await 4 (G_1 G_1G_- g_1g G_2) × 4 (r_1–r_4) = 16 different types in this group (or 3 × 4 = 12 different types)

Can we distinguish between these 16 + 16 = 32 (or 9 + 12 = 21) male types and if so what are the frequencies in the population?

In order to study this question I have tested medical students who studied at the department of ophthalmology of the University Hospital in Oslo 166 males and 25 females

There is one more question which needs consideration Why is deuteranomaly more frequent (5 per cent) than protanomaly (1 per cent)? In the author s opinion as mentioned in the Introduction the protan family is depedent upon the G_1 gene whereas the deutan family is dependent upon the G_2 gene A mesan family would be dependent upon the G_m compound and possibly also upon the g_m compound As the G_1 group has been supposed to be composed of approximately two thirds of the normal individuals and G_2 one third there will seemingly here be a discrepancy which demands an explanation.

A hypothesis which could be proved through investigation allows for the division of the deuteranomal into two groups One group will in combination with G_2 give an exact value for the equation for instance at mark 20 with the mixing screw whereas the other group will yield a more indefinite value for instance in the zone at 10-30 Whereas the allele giving normal colour vision is called n (as before) an allele which gives the smallest deviation from normality is called r_1 *This equation on a point is dependent upon the least reduction of the green valence* the least reduction of the chlorolabe pigment The other group is then conditional upon an r_2 gene (a greater reduction) r_3 giving extreme deuteranomaly and r_4 giving deuteranopia In combination with G_1 they should give the corresponding group of properties described for the protan family But then I have the additional hypothesis that G_1r_1 gives a colour vision property in the male characterized by a normal reading of Ishihara and a Rayleigh equation within the limits of normal variation Therefore this male will usually be diagnosed as normal But when we make the yellow light (589 nm) in the lower semi-circle darker it is possible to find a semiprotanomal equation If the figure on the mixing screw

for a G_1 observer as 37–38–39 and for a G_2 observer 40–41–42 it may be possible for these observers to obey equation at 44 (45) with the dark yellow More im portant for the diagnosis G_1r_1 is a yellow point which distinctly is at shorter wave lengths than normal and a blue point at longer wavelengths than normal The ge nes G_1 and r_2 in combination is then supposed to give the usual protanomal pro-perty

We may ask if it is in order to make a differential diagnosis between those diffe rent degrees of colour vision defect A normal variation in the phenotypes could give overlapping between the types as decided per definition Different anomalo scopes and different investigators could give different results It is also note worthy that an observer by using more than the foveal field will be able to dis criminate colour better than with the central field only This can move the obser ver' to a lesser degree of colour vision defect

If we describe the types G_1 and G_2 with the genes at the two mutons thus G_1g and g_1G_2 we would assume that the types G_m and g_m (G_1G_{-} and g_1g_{o}) are produced through crossing over between the two mutons $G_1g_{-}/g_1G_2 = G_1G_2 + g_1g_{o}$ This would of course be a very rare occurrence but in thousands *and millions of years the compound hemizygote types would increase in frequency* up to a balancing point If we started with an equal frequency of G_1 and G_2 this balancing point would occur when the four chromosome pictures G_1g_2 g_1G_{-} G_1G_2 and g_1g_{-} have the same frequency

The ten possible genotypes for females will then have these frequencies 0 0625 i e. 6 25 per cent G_1g_{-}/G_1g_2 g_1G_2/g_1G_{-} G_1G_2/G_1G_2 and g_1g_2/g_1g_2 that is for the homozygotes The frequency for the six others will be 12 5 per cent that is first for G_1g_2/G_1G_2 G_1g_2/g_1g g_1G_2/G_1G_2 and g_1G_2/g_1g_2 Evidently a cos sing-over in these eight types will give the same two chromosome pictures as be fore the crossing-over But for G_1g $/g_1G_{-}$ the crossing-over will give the pictures G_1G_{-} and g_1g_{o} whereas for G_1G $/g_1g_{-}$ a disunion will be the result As both these genotypes have the frequency 12 5 per cent we will here have the postulated balancing point in which G_m and g_m will neither increase nor decrease

Mutatis mutandis the B genes show the same calculations

Taking into consideration both the G and B properties the males who con stitute the main objects of the investigations in this Part II will have these 16 dif ferent normal genotypes

G_1g_{o}	B_1b_2	phenotype	G_1B_1	g_1G_2	B_1b_2	phenotype	G_2B_1
»	b_1B_2	»	G_1B_2	»	b_1B_2	»	G_2B_2
»	B_1B_2	»	G_1B_m	»	B_1B_2	»	G_2B_m
»	b_1b_2	»	G_1b_m	»	b_1b_2	»	G_2b_m

G_1G_2	B_1b_2	phenotype	G_mB_1	g_1g_2	B_1b_2	phenotype	g_mB_1
»	b_1B_2	»	G_mB_2	»	b_1B_2	»	g_mB_2
»	B_1B_2	»	G_mB_m	»	B_1B_2	»	g_mB_m
»	b_1b_2	»	G_mb_m	»	b_1b_2	»	g_mb_m

The underlined phenotypes are the old types (from 1967 and 1968) whose properties should be well known Also the awaited properties for the other phenotypes within the first two quadruplets should be clear Thus G_1B_m will have a normal G_1 type i e pure green at 515 nm and a pure blue point in the middle between the points for B_1 and B_2 individuals I shall also expect (practically) the same picture for the phenotype G_1b_m We shall have corresponding expectations for the last eight phenotypes It is only important to lay stress upon the expected likeness or resemblance between a G_m and a g_m property and between a B_m and a b_m property But a search for differences will give the possibility of making specific diagnoses

It is important to bear in mind that the crossing over idea is not the only explanation The same result would occur through an event as rare as the crossing over that is a mutation (from G_1g to G_1G_2 or from g_1G_2 to G_1G_2)

I should like to clarify the idea of a mutation If G_1 and G make use of arginine as the amino acid which produces an imine bond to the retinene a mutation that is a fault in the reproduction could *bring about the production of the pyrimidine* thymine instead of the pyrimidine cytosine We would then get histidine (messenger code CAU) instead of arginine (code CGU) Histidine can not form an imine bond with retinene but a single bond and thus could be supposed to slow down *the proton movement as described in Part I This could correspond to a recessive* gene for G that is a g gene also to a recessive gene for B that is a b gene It could be assumed that other mutations could lead to a lethal or a semi lethal situation (effect) especially if these chromosome pictures $g_1g_{_}$ and b_1b_2 were found in the *respecting cistrons The retinenes could be thought to be necessary for the deve* lopment of the foetus in that there must be at least one histidine in the protein (the opsin) The genes would be conveyed through heterozygotic females to their sons. But the rare double homozygotic females g_1g /g_1g ~ b_1b_2/b_1b_2 would *also show a lethal effect, where none of these eight g s and b s had a histidine*

As an aside I should like to discuss some of the questions which will have occurred to the observant reader How can it be that types G_1G_2 (G_m) and g_1g_2 (g_m) among males, which now are supposed to be so common were not found in *my 1967 paper and the corresponding B types were not found in my 1968 paper?* In the last paper some figures indicated that something was wrong with the supposition of there being only two types of males B_1 and $B_{_}$ but a great deviation from the expected was not found to be impossible (See pgs. 11–12 in Waaler *1968)*

That I did not find the G_m g_m B_m and b_m types at that time was obviously a fault which can be explained by the biased opinion (Homines quod volunt cre dunt) There should only be two G types and only two B types among males

When I made the G diagnoses by means of the nine equations I could begin with a G_1 value at the first equation and therefore expect the eight following equ ations to correspond to this diagnosis If the diagnosis really should be G_m the values will tend to slope upwards towards the G_- values passing through the fifth equation with ambiguous values Here I have repeatedly mentioned that this fifth equation often gave uncertain values as to the bimodality (G_1 and G_-) and that these observers (G_m) gave different answers to the equation when we moved from *the green side or from the orange side They thus would not return to the same* point as usually expected for the true G_1 Therefore it became possible for the investigator to accept a value convenient for his preoccupied opinion The same *was true for a B_m observer He was unable to reach the same point from the blue* green side and from the side of lilac and the investigator could select the value nearer to one of the two supposed averages This is of course no excuse for the investigator only an explanation

Probably the same reasoning will also apply for the g_m and b_m observers

In another aside in this connection with the above mentioned difficulty we can discuss the bimodality of G values at the fifth equation The G_m (and gm) (male) observers have their nine equations sloping from low G values at the first equation to high values at the ninth Other types especially G_1r_1 show the same oblique course in the nine equations An investigator who works with the normal Rayleigh equation in a mass investigation will therefore probably not find any bimodality Furthermore the fact that some investigators do not find a bimo dality of the unique green whereas others do may be explained through the dif *ferent methods of the investigators Those who work with a yellow light near 589* nm (as in a usual Nagel s anomaloscope) will fail to find a bimodality whereas in vestigators working with a yellow light near 574 nm (that is near the place of my first equation) will more easily find such a bimodality

After these asides we shall study the facts found during investigations on the 166 male and the 25 female medical students The female students were tested only because I did not like to tell that I was not interested in them[1] I had no in tention of making conclusions from this sparse material Therefore I only refer the results. Two of them were diagnosed as conductors(see Waaler 1969 and 1973b) Twenty three were diagnosed as 12 G_1/G_1 (of them 6 B_1/B_1 1 B_1/B and 5 B_2/B_2) 8 G_1/G (of them 2 B_1/B_1 4 B_1/B_2 and 2 B_2/B_2) and 3 G_2/G_2 (1 B_1B and 2 B_2/B_2)

The 142 males with normal colour vision had these diagnoses

31 G_1B_1	21 G_1B_m	19 G_1B_2	that is 71 G_1
19 G_mB_1	13 $G_m B_m$	10 G_mB_2	» 42 G_m
15 G_2B_1	5 G_2B_m	9 G_2B_2	» 29 G_2
that is 65 B_1	39 B_m	38 B_2	» 142 males with normal colour vision

Table 3

The 24 males with colour vision defects were given these diagnoses according to the test results

G_1r_1	7 cases	This is an important novelty The correct figure may be greater as in the beginning I had not discovered the importance of the yellow point the movement of which to shorter wavelengths would ensure the diagnosis
G_1r_2	2 cases	protanomaly
G_2r_1	7 cases	near points of equation } deuteranomaly
G_2r_2	3 cases	zones of equation. } deuteranomaly
B_2r_3	1 case	extreme deuteranomaly
G_2r_4	1 case	deuteranopia.
G_mr_1	3 cases	mesanomal They have the normal Rayleigh equation and the normal Ishihara reading But their green valence reduction is shown by the distinct movement of their yellow point to shorter wavelengths, and also by their broad nine equations These are two methods of investigations, which are not used by others

Table 4

It is clear that the question why there are more deutans than protans in spite of there being more G_1 individuals than G is not completely solved Yet, the new first mentioned group G_1r_1 has greatly changed the total picture

I tried different ways and presuppositions for calculations more or less like the calculation made in the beginning of this Part II leading to a balancing point, where the union of G_1 and G_{-} in one cistron and the disunion had the same frequency

One of these studies had this basis G_1 and G_{-} were supposed to be 52.5 and 47 5 per cent respectively before the crossing over occurred Through this crossing over types G_m (G_1G_2) and g_m (g_1g_{-}) were formed It was assumed that the gene complex g_1g_2 was lethal (the foetus would not grow to the adult stage) When a balancing point was reached the frequency of G_m among males would turn out to be as great as the sum of G_1 and G i e both around 50 per cent

An other basis for calculations was that the usual g_1 and g_2 corresponding to

histidine as G_1 and G_2 corresponded to arginine The complex g_1g_2 would in males lead to a slower but balanced development of the properties But other mutations were assumed to be lethal The sum of the G_1G_2 and g_1g_2 types was again around 50 per cent when approaching a balancing point.

I tried different assumptions for the frequency of lethal genes And at last I tried the supposition that G_m and g_m were not produced through crossing over at all but through mutation (from G_1g_2 to G_1G_2 for instance and mutation back again from G_1G to g_1G_2 or G_1g_2) Also with the last supposition the sum of G_m and g_m would be around 50 per cent, i e alike the sum of G_1 and G_2

None av these ideas could lead us to frequencies as those found among the 142 students (Table 3)

A hypothesis (in addition to the many others I have proposed!) suggests that the g_1 gene dominates (or sometimes partly dominates) over the g_2 gene The g_1g_2 complex will then be unbalanced and the yellow valence curve will more or less be similar to this curve for the G_1 observers The presence of a B_m gene will make the diagnoses uncertain as for these observers the points of pure colour will be ambiguous If we therefore exclude the 39 cases (Table 3) which are complicated with the presence of a B_m gene we get for G_1 31 + 19 cases, for G_m 19 + 10 cases and for G_2 15 + 9 that is 50 29 and 24 cases These figures could in fact be an occasional distribution of 25 G_1 + 25 g_m (sum 50) 25 G_m and 25 G_2

Is there now any difference between the two groups included in the 50 G_1 diagnoses? My diagnoses are based upon the nine equations If in addition I tried to verify the real green point at 515 or 525 nm (or 520 for G_m), I have noticed that the green point is always relatively sharp from the blue green side but not so sharp from the yellow side In some cases the observer did not per ceive yellow before we were well away from the green point where the blue dis appears This could indicate a weak yellow valence curve I have no proof of these observers being the group g_1g_2 as I did not notify any defect in yellow perception for each observer

Conclusions from this Part II would therefore be 1) that assured G diagnoses (G_1 G_m or G_2) are not really easy and 2) that we in the g_m group have a problem for the future

There is also a third conclusion founded upon the new pseudo-normal or semi normal type G_1r_1 All observers reading Ishihara with both the normal and some of the figures intended for the colour blind should be regarded with suspicion in this direction

But if we may now believe that G_1 and G_2 have about the same frequency (1 1 and not 2 1 as usually presumed) we find that the figures in Table 4 correspond very well to those expected, when we include this new type G_1r_1 Thus we have solved the problem 'why deutan is more frequent than protan It is not!

PART III.

PROTAN DEUTAN CROSSING OVER

The locus of the colour blindness is a marker on the map of the X-chromosome, and thus the localisation of this gene is important. We must here draw attention to that the more important markers will be those concerning the four properties of the two green (G_1 and $G_$) and the two blue (B_1 and B_n) points in the spect rum (Waaler 1967 1968 1969 1973a and 1973b) This is because they are the major properties found in 92 per cent of all males whereas colour blindness will only be found in 8 per cent. However a discussion concerning the localization of the genes responsible for colour blindness will be interesting and especially so the distance between the protan and deutan loci

An attempt has been made to find the distance between colour blindness genes and the G6PD gene Porter et al (1962) estimated (as quoted from Kalmus (1962) that the recombination fraction between the genes for glucose-6-phos phate dehydrogenase deficiency and that for deutan defects as 0 05 (between 0 009 and 0 18 at 90 per cent confidence level) and the 90 per cent probability of recombination between the glucose 6 phosphate dehydrogenase gene and a protan gene as less than 0 2 and they considered their results insufficient to decide be tween the two loci and one locus hypotheses This would mean that the loc ations of the protan and deutan could lie close to one another But Kalmus con tinues However considering Vanderdonck and Verriest s pedigree it is at pre- sent reasonable to assume that the protan locus and the deutan locus are not very close and that perhaps the locus for G6PD lies between them probably near to the deutan locus Siniscalco et al (1964) have said that an interesting pedigree of theirs throws light upon this particular issue and strongly supports Dr Kal mus conclusions

From the above reported experiments, it is evident that the demonstration of this protan-deutan distance is of the greatest interest. Crossing over might be in vestigated when females of a protan/deutan genotype have more than two sons Females of this genotype usually have normal colour vision

If a female with normal colour vision has two sons with the same protan type or the same deutan type she could be a conductor (heterozygous for the particu lar gene) or a protan/deutan genotype If she has a protan and a deutan son she certainly has this compound genotype However these cases will tell us nothing about the crossing-over percentage We have the possibility of finding a crossing-over only when such a mother has more than two protan and deutan sons If we find such a case of crossing over and place figure 1 in the numerator we will not have the faintest idea of what figure to use for the denominator It might be 1000 In a population of 40 millions i e 20 millions females, a 1000 such mothers with more than two sons would not be an unlikely figure

Interesting speculations concerning this problem can be found in a report by Fraser (1969) The difficulty lies in the 'ascertainment of informative families He proposes corrections for families with two three or more sons when there are always at least one protan and one deutan son and he bases his calculations upon a group of 12 families in a companion paper (Thuline et al 1969) Using three methods he calculated the estimates as being 0 064 0 071 and between 0 08 and 0 09 although he admitted that 0 08 might have been an overestimate Table 2 in the work of Thuline et al contains 21 families but only 12 of them were ascertainable. (Later Adam (1970) has published two such ascertainable families each with one protan and two deutan sons) This table contains four columns the first for number of sons (from three to five) the second and third columns total protan and deutan respectively and the fourth normal colour vision or compound hemizygotes both indicating crossing over In the last column the figures are ten times 0 for family 14 it is 2 and for family 20 it is 1

In my opinion there is one additional case of interest Family 16 (Pickford 1962) has three different sons with Pa, Da, and EDA Although there are two deutan and one protan son there must also here be a case of crossing over

These three cases shall be discussed in relation to the new image of the colour vision region (Waaler 1973b) There are three neighbouring cistrons (not necessarily adjoining) one cistron having the G genes (on two mutons) G_1g_2 G_1G_2 (called G_m) g_1g_2 (called g_m) and g_1G_2 the second cistron having the B genes on two mutons B_1b_2 (phenotype B_1) B_1B_2 (phenotype B_m) b_1b_2 (called b_m) and b_1B_2 (phenotype B_2) and finally the third cistron with the genes reducing the number (or effect) of the B dependent cones with green absorbing pigments i e the chlorolabe cones These last genes were originally (1973b) supposed to be four quantitative genes n (for the normal colour vision there being no reduction) 1 for a reduction leading to protanomaly in connection with G_1 and deuteranomaly in connection with G_2 gene e giving extreme protanomaly (EPA) and deuteranomaly (EDA) and finally gene p giving protanopia and deuteranopia In part II these genes were hypothetically changed to five genes n r_1 r_2 (instead of 1) r_3 for e and r_4 for p But here in Part III I will retain the first designations because here in the cases of other authors I have no possibility (however see pedigree C at the end of Part III) of diagnosing the two degrees of anomaly (r_1 and r_2 for 1) Further the whole is simplified by leaving out the B cistron because the genes here have little influence on the colour blindness properties.

The heterozygote females G_1/G_2 (G_1g_2/g_1G_2) give reactions between those for the G_1 and G_2 as also do the G_1G_2 males (both groups having two different yellow valence curves) Therefore we have three rows of genes (and therefore twelve male properties)

Normal G_1	PA	EPA	P
Normal G_1G_2	mesanomaly	EMA	mesanopia
Normal G_2	DA	EDA	D

Particularly noteworthy is the mesanomal group The males here read Ishihara as normal and their Rayleigh equations are normal or near the borderline of the normal variation

From the point of view of these images of the colour vision region I shall now discuss the three above mentioned families In the same way I shall also discuss the three pedigrees from a great family group in Venezuela of which I later re ceived information

1 The case of Pickford (1962) is described in his Pedigree I and his Fig 1 The father has normal colour vision whereas the mother is deuteranomal (DA) There is a daughter with normal colour vision and three sons a deuteranomal (DA) an extreme deuteranomal (EDA) and a compound hemizygote for PA and EDA confirmed as he had characteristics of both conditions I accept the diagnoses (phenotypes) of Pickford and also the genotypes as described in his Fig 1 that is that the mother has the PA linked with EDA in one of her X chromosomes whereas she has DA in the other Two of the sons have each re ceived these two X chromosomes a DA son and the compound hemizygote son who had characteristics of both conditions We then have Pickford s clear con clusion that crossing-over needs to have occurred for the production of the EDA son With the mentioned colour vision region image we have the mother s two X chromosome regions described thus G_1G_2 e (extreme mesano mal) and G_ 1 (deuteranomal) (NB' I dominating over e) With crossing over be tween the $\bar{G}$ cistron and the I e p cistron we might get an X chromosome G_2 e (extreme deuteranomaly) that is the crossing over is inter cistronic not intra cistronic

I lay setress upon the fact that there is no discrepancy between Pickford s line of argument and my own

2 The next case is the family described by Siniscalco et al (1964) in which there were a male propositus (proband in the problem of the G6PD locus) who was a protanope as was his maternal grandfather He had a deuteranope brother and two deuteranope maternal uncles Thus it is quite clear that the mother with normal colour vision had the gene for deuteranopia in her maternal X-chromosome whereas she had that for protanopia in her paternal X chromosome But then there was a third son who gave reactions in the anomaloscope and in Farns worth Munsell 100 Hue Test which placed him between protanopia and deuter anopia 'The obvious conclusion is that he is carrying the genes for both protan and deutan colour blindness

This would be a result of a crossing over and the findings correspond to mes anopia as described by Waaler (1973b) The mother s genotype is illustrated through these two colour vision region images The X chromosome with G_2 p (from her mother and to her two brothers and to the first mentioned brother of the propositus) giving the property of deuteranopia and the X chromosome with G_1

p (from her father and to the propositus) giving the property of protanopia. If we use the complete description of the two mutons in the G cistron as shown in the Introduction G_1g_2 and g_1G_2 we would suppose that we would get two different results of the crossing-over, that is G_1G_2 and g_1g_2. In this Part III, it is convenient to use only G_1G as the description of the genotype. The colour vision region of this third son would be G_1G_2 p (or G_m p)

Although a hypothesis of a mutation (from G_1g, to G_1G_2 or from g_1G to G_1G_2) probably would be as frequent I would accept the conclusion that we have here a crossing over between protan and deutan that is an intra cistronic crossing-over between G_1 and G_2

The G_1G_2 compound hemizygote with n gives a G_m male with normal colour vision whereas together with the alleles l e and p it should give mesanomaly extreme mesanomaly and mesanopia respectively

In the same paper they discussed the relation to the locus of G6Pd. They made the 'tentative conclusion that 'the sequence of the three loci in question may be

Deutan—0 04—G6PD—0 05—Protan

As mentioned above in connection with the papers of Porter et al (1962) and Kalmus (1962) the investigations themselves give no evidence against the following link up occurring

Protan—0 01—Deutan—0 04—G6PD

Anyway this important investigation might be in accordance with a short distance between P and D that is between G_1 and G_2

3 Finally we have come to the family 14 in the Table 2 from Thuline et al 1969) This family is described by Vanderdonck & Verriest (1960) and is here presented as a pedigree in Fig 10 below

Only I_2 is not tested. All the others are tested with Ishihara (1) Pollack (2) tritan plate of Farnsworth (3) a pseudo-isochromatic table of Hardy Rand and Ritter (H R R) (4) the panel 15 of Farnsworth (5) the 100-Hue Test of Farnsworth Munsell (6) and a Nagel s anomaloscope (7)

In the Fig 10 the diagnoses (phenotypes) are placed within the quadrangles (for males) and circles (for females) N D and PA. The genotypes according to the colour vision region are placed near below or at the side of the mark for the individual observers.

Immediately we find two very unusual diagnoses here that is in the case of the mother II_2 and her daugher III_4. Both have the property of protanomaly. The mother with a deuteranope father (D) and a protanomal son (PA) must have the genotype PA/D and all information in the literature indicate that a female with this genotype should be expected to have normal colour vision. The daughter with a normal father II_1 (N) probably has the genotype N/PA that is she is a

conductor for protanomaly and should also be expected to have normal colour vision

The authors mention cases in the literature indicating the possibility of cases which manifest the dominance of the gene for protanomaly

They mention the paper of Pickford (1962) which has two other Pedigrees, II and III described after the above discussed Pedigree I Pickford here obviously gave explanations quite in accordance with those given below for the discussion of this family of Vanderdonck & Verriest Particularly Pickford assumes that both fathers (believed normal) are compound hemizygotes for PA and DA that is, they are mesanomal Such types give reactions both in Ishihara and in the anomaloscope which could indicate normal colour vision Furthermore the daughter in Pedigree III has, in Pickford s explanation the genotype supposed by me for III_4 and has (as this III_4) the property of protanomaly

Vanderdonck and Verriest further mention a family of Jaeger (1951) But this author explains the unusual reactions as being due to the property of tritanomaly which in this case is combined in two sisters with the properties of protan and deutan This family cannot definitely confirm the explanation of the authors (V & V)

The authors (V & V) find that the pseudodominant manifestation of the prot anomaly gene of II_2 seems to be made probably through the protanomaly of the daughter III_4 In other words the two unusual diagnoses are used to make the explanation more probable for each other Of course they may be right but for

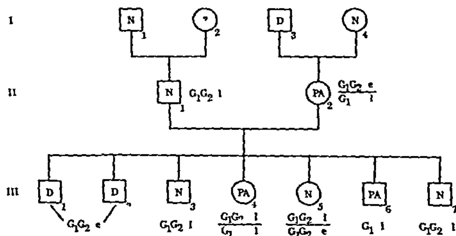


Fig 9

Fig 10 The pedigree from Vanderdonck and Verriest

me however two such extraordinary cases are a temptation for trying another explanation

Some of the other cases also give suspicion of another diagnosis The deuter anope grandfather I_3 has his equation in the red (90) at mark 22 of the yellow brightness screw and the equation in the green at mark 19 of the yellow light in tensity This is contrary to what is usual for a deuteranope observer, who usually uses darker in the red and lighter in the green It is also noteworthy that the three normal II_1 III_3 and III_5 have remarkably many faults in Ishihara and Pol lack, III_5 also has an unusually high chiffre index in the 100 Hue Test

The most important fact in the family is that the mother II_2 besides having two deuteranope sons and a protanomal son also has two sons with normal colour vision III_3 and III_7 They both provide proof of a crossing over having occur red between a protan and a deutan gene The younger of the two age 5 ½ year has not been measured with the anomaloscope 'parait normal, and has not been tested with the 100 Hue Test In the panel 15 he makes three minor errors, although he might still have normal colour vision The other brother III_3 might also be normal although he makes four erreurs de structuration in Ishihara and seven in Pollack.

My hypothetical explanation is that the grandfather, I_3 is an extreme mesano-mal (EMA) that is he is a compound hemizygote with EDA and EPA the first giving equations from green to the normal Rayleigh and the other from this nor mal middle matching point to red Thus he could be supposed to give equations very similar to those of a usual deuteranope The same would then also be the ge notype and phenotype for the daughter s sons III_1 and III_2 These three males should then have the following picture in the colour vision region G_1G_2 e

The mother could then have these two pictures of the colour vision region G_1G_2 e and G_1 l The second chromosome has gone to the son III_6 who is prot anomal The mother herself will have the phenotype protanomaly (or nearly so) because l dominates over e

By inter cistronic crossing over (NB! not intra cistronic) we may get an X chromosome with the region G_1G_2 l which is assumed to give the phenotype of mesanomaly (MA) which might in turn give reactions indicating normal colour vision

We might also suppose that the father II_1 has the genotype of mesanomaly The daughter III_4 might then have the two X chromosomes with G_1 l and G_1G_2 l the first coming from her mother whereas the second will come from her father This will give the phenotype of protanomaly or quite nearly so

The daughter III_5 receives the G_1G_2 l pattern from her father and as she is supposed to have received the EMA chromosome G_1G_2 e from her mother and as l dominates over e the result will be mesanomaly The four normal in dividuals II_1 III_3 III_5 and III_7 are in this way supposed to be mesanomal

Altogether our conclusion agrees with that of the authors crossing-over for the two sons and III_3 and III This in an inter-cistronic crossing over between the G cistron and the l-e p cistron

To the twelve families analysed by Fraser (1969) and by Thuline et al (1969) it is natural to add the two (in parenthesis) mentioned families of Adam It is also reasonable to add a colour blind family (from Waaler 1969) where a mother and two of her daughters with normal colour vision have the genotype protanopia/deuteranopia. As there are the same genes for both protanopia and deuteranopia in these three females, it is natural from a statistical point of view to call this one an ascertainable family with five sons two protan and three deutan

Therefore in 15 ascertainable families there is one case of intra-cistronic crossing-over between G_1 and G_2 which from the point of view of the one locus hypothesis (Waaler 1927) and the modern one cistron hypothesis (Waaler 1973b) is the real protan/deutan crossing over

A year after I had finished these speculations upon the for me until then known cases of protan-deutan crossing over I received four papers from Sergio Arias and Alvaro Rodriguez (1971 1972 1973a and 1973b) They describe an inbred isolate of German ancestry called Colonia Tovar in Northern Venezuela which has been studied genetically during the last three years (1973a) 'The aim of this paper is to report findings on dyschromatopsic subjects from some kindreds in which one identical gene for extreme protanomaly is present in various combinations with different deutan genes, giving a basis for the phenotypical identification of compound hemizygotes providing too new information for a better estimation of the recombination fraction of the two colour vision loci Complete selection for the protan gene was intended when we realized protans were very rare in the population It came out thereafter that only descendants of one couple married 110 years ago were carrying the gene

These quotations show clearly the really fantastic population which was studied with Ishihara H R R plates Farnsworth F 2 plate the Farnsworth Dichotomours test (D 15) and the Pickford Nicolson anomaloscope It is important for the reader (it has been so for me) to study the paper describing this anomaloscope of R. W Pickford & R. Lakowski (1960)

Out of this family complex, put down in a circular form (Fig 1 1973a) they have extracted three pedigrees (A B and C in 1973b) In table 1 of the 1973a paper we find all of the important results, for one thing the reading in Ishihara (normal protan deutan unclassifiable) and the Pickford range, that is the range of the equations in the anomaloscope The anomaloscope (by P & L 1960) has a normal matching point (Rayleigh equation) at 37 4 ($\pm$ 1 25 standard deviation)) and a scale from 0 (red) to 80 (green) In the paper of A & R (1973a) 35 is said to be the normal matching point

The usual definition of extreme deuteranomaly and protanomaly is that the observers have equations in a broad zone from the normal matching point to 80 and 0 respectively There might be variations on both sides of this range as it might happen that the equation range does not reach the respective end point It might also happen that the equations are found far to the other side of the normal matching point the Rayleigh equation

The seven observers who have the Nicolson diagnosis EPA in Table 1 (A & R 1973a) have these Pickford ranges 0-80 18-80 20-60 0-70 20-80 15-80 and 15-80 The first and fourth have equations to 0 (red), but this 0 is only found after colour fatigue In a letter from Arias he writes All of them are able to see color differences (and to name them correctly) at a redder end below 18 and most of them already below 20 From this I conclude that these seven at any rate are not typical examples of the extreme protanomal type When they also have equations up to 80 (five of the seven) and 70 and 60 they are atypical at the green end too

The four males having been finally diagnosed as compound hemizygotes have a combination with a deutan gene They have the ranges of 48-80 (combination with D) 38 5-43 (combination with DA) and 35-42 and 39-42 for a propositus and his maternal grandfather For these two the deutan gene is either DA or EDA

These four observers have (before the final diagnosis) received the Nicolson diagnosis, EDA for the first and DA for the last three And this discrepancy between the final and the Nicolson diagnoses proves the compound hemizygotic constitution I agree completely in this line of argument

If I now shall explain where I disagree I shall first particularise the two conceptions of extreme mesanomaly and mesanopia from the idea of the colour vision region I am not certain that we are able to make the differential diagnosis among observers belonging to these two genotypes The sum of the effect of EPA and EDA in the extreme mesanomal EMA would be supposed to give equations from red to green in the anomaloscope We also would expect a similar effect from P and D together in mesanopia

Furthermore I should like to repeat (from my 1973a paper) the description of two cases where I have made the diagnosis mesanopia These subjects read Ishihara as a protan They did not easily succeed in getting equations in the anomaloscopic red end but they both obeyed equations at the green end Here we have the important fact that they came to the mark 26 5 on the scale for the intensity of the yellow light whereas a deuteranope usually comes to 20 and a protanope to 40 that is clearly between the values for the deuteranope and protanope In a communication from Arias I was told that the scale value for the yellow light intensity for his EPA that is the family type, is 34 as an average whereas a deuteranope on his anomaloscope has a value below 30 typically at 27

He could not tell me what the customary value for an ordinary protanope obser ver ought to be But we are here at the point of my disagreement In my opinion the characteristic gene that has passed through four–six generations from the female married 110 years age, is already a compound gene

Thereafter we can study the three pedigrees (A B and C) where I have ac cepted that a crossing over has occurred

Pedigree A The proband has six brothers three diagnosed as deuteranomal (DA) and three as extreme protanomal (EPA) with the picture described above a picture which has brought me to propose that such observers already have pro-tan and deutan in their single X chromosome They should in the language of the colour vision region (without the B cistron) have their region described thus B_1G_2 e Their mother should therefore have these two X-chromosomes G_2 l and G_1G e The maternal grandfather of this proband is the son of the female who was married 110 years ago and who is supposed to have introduced this charac teristic gene into the great inbred family

Through a crossing over between the G cistron and the l e p- cistron we might get the X chromosome G_1G_2 l which is the supposed genotype of a mesano-mal Concerning this type I have already said that a mesanomal observer might appear to be normal as judged by both the Ishihara and the anomaloscope test. The propositus of the family is not normal however With Ishihara he appears to be a protan his range is 38 5–43 as the basis for DA diagnosis But two of the three brothers (the third is not tested) have the usual deuteranomal ranges of 45–50 and 47–51 And then I remembered that these mesanomal individuals were first called by me (1969) Low degree deuteranomal and they had a normal Rayleigh equation However in the first of my nine equations where the yellow colour has the wavelength 574 nm they gave a deviation from normality in the same direction as for the usual deuteranomal Here we may remark upon the difference in the anomaloscope used Whereas in my Nagel s anomaloscope the three lights are nearly monochromatic the three colours in Pickford s anomalo-scope have been produced by light over a greater part of the spectrum This is not a drawback or a deficiency of the Pickford apparatus quite the contrary as we just have seen we might find the diagnosis using his anomaloscope On the other hand with my anomaloscope the individual will not be discovered in a mass investigation (The diagnosis might, in my anomaloscope be confirmed by fixing the observers point of pure yellow at shorter wavelengths than normal) The wavelengths for the yellow green and red at the place of the first of my nine equ ations are more alike the dominating wavelength of Pickford It seems there fore reasonable to assume that the diagnosis really is mesanomaly with the pat tern in the colour vision region G_1G_o l

Pedigree B Here there are three brothers one being a typical deuteranope (D) with this pattern of the colour vision region G_2 p one having the family

EPA supposed by me to have the X chromosome colour vision region G_1G_2 e Their mother is through them analysed to have the two X chromosomes of G_2 p and G_1G_2 e The mother is a protan/deutan heterozygote in repulsion She has normal colour vision because she has two different yellow valence curves

The third brother the propositus, has the Nicolson diagnosis EDA with his range 48–80 he is unclassifiable in Ishihara but read H R R plates as protan Again there is the discrepancy between the pseudoisochromatic tables reading and the anomaloscope testing which shows that a crossing over has occurred here I agree with this conclusion but accept the anomaloscope diagnosis EDA which here is the result of a crossing over between the G cistron and the l e p cistron in the X-chromosomes of the mother resulting in the colour vision region G_2 e i e extreme deuteranomaly The differences between the reactions with Pickford s and my anomaloscope is discussed under pedigree A

Pedigree C Here the crossing over has not occurred between the mother s X chromosomes. We see that this proband and his maternal grandfather obviously have the same phenotype range 35–42 for both They again have a very Low degree of deuteranomaly We find as so often is the case in colour blindness that a conductor mother has transmitted the gene from the grandfather to his daughter's son and thus he should be regarded as the real proband in this pedigree In the family tree down to the inductor of the family gene (III_{12}) we have for the three pedigrees

A		B		C	
	VI_{17}		V_{49}		IV_{15}
	V_{13} mother s		IV_{26} mother s		III_9 mother's
	IV_{13} father's		IV_{25} mother s		IV_{21} mother s
	III_{12} mother		III_{12} mother		III_{12} mother

This maternal grandfather IV_{15} the real proband has two brothers This family is important because the authors (A & R 1973a) will show that we have two cases of crossing over in the same kindred However I have here another explanation One of the brothers has the family gene with the Ishihara protan reading and the Pickford range 0 (after fatigue) 80 that is G_1G_2 e To explain the facts in this kindred I must go back to Part II where I divided the l gene into two degrees of reduction in the green valence that is r_1 and r_2 G_2 r_1 gives a deuteranomaly with a narrow range (a point) whereas G_2 r_2 gives a deuterano maly with a broader zone of equations G_1 r_2 gives the ordinary protanomaly, whereas G_1 r_1 gives such a low degree of deviation from normality that such an observer in a mass investigation might be said to have a normal Rayleigh equ ation although his zone might be found to go a little outside of the normal variation

If I now assume that the mother (III_9) (not tested) has these two pictures in

the colour vision region of her X-chromosomes G_1G_- e and G_1 r_1 I shall suppose that the third brother has received the last chromosome and is called normal performed all tests correctly The crossing-over between the G cistron and the l e p (r_1 r_4) cistron might give G_1G_- r_1 which is the genotype of the mesanomal With regard to this property I refer to the discussion concerning the pedigree A family

The old mother III_9 has three sons

IV_{15} the crossing-over case with the chromosome picture G_1G_2 r_1 (or l) that is, a mesanomal see Pedigree A.

IV_{17} EPA G_1G_2 e (the family complex)

IV_{18} called normal by me diagnosed as the new semi normal protan type G_1 r_1 The mother is analysed as having the two last gene complexes in repulsion

In conclusion this very interesting family group from Venezuela has been studied in view of the colour vision region The three cases of crossing over (one in each pedigree) are shown possibly to be inter-cistronic between the G cistron and the l-e p (r_1 r_4) cistron and not intra-cistronic between G_1 and G_2 which to the author s point of view is the real protan-deutan crossing-over

SUMMARY

1 Protan and deutan are localized in one cistron

In 1925–26 it was found (Waaler 1927) that there existed two series of allelic genes which produce the different degrees of colour vision defects One series was responsible for protanomaly (PA) extreme protanomaly (EPA) and protanopia (P) the other DA EDA and D (with the corresponding abbreviations used in the literature) In both these series the dominance of the genes occurs in the following direction PA > EPA > P and the two series are called protan and deutan A female with a protan gene in one of her X-chromosomes and a deutan gene in the other turned out (Waaler 1927) to have normal colour vision At that time the natural explanation of this fact was that protan and deutan as genes were placed at two loci (Waaler s two locus hypothesis) but in spite of that, the author (1927) proposed as his favourite idea that there might be only one locus for protan and deutan with mutations at two different places of the great gene molecule The cistron is the part of DNA in the chromosome which is responsible for the hereditary property studied whereas the muton is the small part which undergoes a mutation The old one locus hypothesis was thereafter modified (Waaler 1968) to become the hypothesis of one cistron and two mutons *exactly corresponding to the illustrating pictures in the 1927 paper (repeated in* the 1967 paper) This was thus a preview of the later cistron conception where the possibility of mutations on different mutons is shown

2 Extension of the protan and deutan series

Later (Waaler 1967) two types were found in male subjects with normal co lour vision The two types were characterized by a perception of 'pure green' at 515 and 525 nm The two properties were designated G_1 and G_2 and so were also their producing genes in the X chromosome Thereafter a new modification entered the picture G_1 becoming the normal link in the protan chain, and G_2 the normal link in the deutan series At the same time the assumption was made that the real colour blindness genes were placed in an other cistron in the X chromosome but that their combined existence with G_1 and G_2 brought about the protan and deutan properties respectively

Furthermore (Waaler 1968) two types with different points of pure blue were found among males with normal colour vision that is at 487 nm (B_1) and 479 nm (B_2) These genes were supposed to be localized in a third X chromosome cistron (the colour vision region) Females might in both cases have three genotypes and also three phenotypes as the heterozygotes (G_1/G_2 and B_1/B_2) gave intermediate reactions

Further, points of pure yellow and points of pure red were found From an individual s yellow point to his blue point there is a green valence curve, with a maximum perception of green in the middle (calculated in terahertz) From an individual s red point to his green point there is a corresponding yellow valence curve

The proper colour blindness genes were supposed to give different degrees of deviation from normal colour vision through degrees of reduction of the green valence Thereby the yellow point moved to shorter wavelengths and the blue point to longer At the same time the yellow valence curve increased in width so it seemed that the effect of these genes was to influence the relative magnitude of the green and yellow valence curves

The last supposition about these green valence reducing genes is that the num ber of the quantitative alleles is five that is n (giving the normal G_1 and G_2 properties) and four genes (reducing the green valence and thereby reducing the colour vision efficiency) that is r_1 and r_2 for two degrees of anomaly PA and DA in combination with G_1 and G_2 r_3 for EPA and EDA and r_4 for protanopia and deuteranopia.

3 The trichromate theory is wrong

The trichromate theory accepted by most investigators seemed to get a sup port in the discovery of three different cones in the (human) retina, which absorb light at three maxima, 447 540 and 577 nm They were called cyanolabe chloro labe and erythrolabe cones because they were thought to capture the theory s three accepted colours blue (blue violet) green and red The absorption curve for the chlorolabe cones agrees with my green valence curve The absorption

curve for the erythrolabe cones however agrees with my yellow valence curve At the maximum of the curve 577 nm (others say 570 nm) we have no sensation of red – the red in orange begins first above the yellow point at about 580 nm Therefore I have renamed this cone a chololabe cone as it captures the yellow We have thus discovered an important fault in the trichromate theory By diagnosing protanopes and deuteranopes with the anomaloscope we find they both obey likeness between yellow and green by making the yellow light more bright, more so for the protanope and they also obey likeness between yellow and red by making the yellow light darker more so for the protanope He who is green blind (the deuteranope) is also red blind and vice versa, the protanope is also green blind The names *protanopia* (*protos*, the first, i e the red component) and deuteranopia (deuteros the second i e the green component) thus demonstrate the incorrectness of the trichromate theory A further proof for the incorrectness of the theory is found in the next point of this summary

4 A modified Hering's theory

The cyanolabe absorption curve with its maximum at 447 nm and its hypothetical porphyrolabe part with a maximum in the infrared crosses the green and yellow valence curves at the points of the pure colours (See Fig 1 in Part I) i.e crossing the green valence curve at the blue points and there counteracting and cancelling the green (pure blue is thus the result) and then counteracting and cancelling the yellow valence at the green points (only the green valence in function) *In addition the porphyrolabe part crossses the yellow valence curve* at the red point and the green valence curve at the yellow point, producing the observer s feeling of colour pureness at both these points This appears as a modification of the Hering theory It is only a modification in that the main principle is retained From the side of the short wavelenghts the blue violet counter acts and cancels first the green and then the yellow from the side of the long wavelengths the red purple counteracts and cancels first the yellow and then the green That light from the two peripheral parts of the visual spectrum have counteracting effect on light in the region of green and yellow is demonstrated by electroretinography (ERG) (Waaler 1973b) The important positive b-wave which occurs as a result of electro-chemical events between the receptors and the ganglion cells in the retina, is changed to an indication of a negative b wave in the peripheral parts of the spectrum To find this important fact it is of no purpose to use ordinary coloured filters I therefore used *specific filters which enables* the passage of a sharp region of the spectrum and practically nothing outside the maximum ± 10 to 15 nm

At the same time as the above facts support the Hering theory they show how the trichromate theory is wrong

5 The pigments in the retinal receptors

There are light absorbing pigments in the rods and cones and they consist of conjugated proteins with a chromophore as the prosthetic group The protein is called opsin and the chromophore group is called retinene In Part I seven different pigments one for the rods and two for each of the three cones are described Both opsins and the retinenes are different, but are able to fit together just as a key in a lock

When the light energy is absorbed by the pigments two events occur Firstly an electrical current is started instantaneously usually as a wave of depolarization in the nerve system i e a decrease in the external positive potential of the cells and axons (The main electrical effects comes from the rods Upon this the effect from the chlorolabe and chlololabe cones act as a positive whereas the effect from the cyanolabe cones act as a negative This is demonstrated by ERG)

The second event is a slower chain of chemical reactions leading to the dissolution of the bonds between opsin and retinene (the well known bleaching of visual purple in the rods) On the surface of the opsin an acid binding group and two or three SH groups are set free

The retinenes are composed of a hexagon and a chain with conjugated double bonds ending in an aldehyde group (See Figs 2–8 in Part I) By the action of isomerases the all trans form is converted to different cis-forms 11 cis (the basis for visual purple in the rods) 9-cis (by me ascribed to the chlorolabe cones) 13-cis (chlololabe cones) and 9 13-dicis (cyanolabe cones) In the 11 cis form there is a steric hindrance for coplanarity of the conjugated chain. This is an explanation, according to the chemists of the broad absorption curve for the rods which occurs all over the visual spectrum The two borders of the visual spectrum are in fact determined by this absorption curve The breadth of this absorption curve is in contrast to the curves for the cones which are narrower over a selected part of the spectrum This difference i according to the chemists because of the non-coplanarity of the retinene in visual purple Another important fact is that there are two different hexagons with a double bond at different places (Figs 2 and 3 in Part I) For one of these types there will be one conjugated bond less than for the other type Thus a difference in light energy is needed for the dissolution of the opsin retinene bond This difference may correspond to the difference of the two maxima for the two green valence curves (connected with the B_1 and B_2 properties and the chlorolabe cones) as well as the two maxima for the yellow valence curves (G_1 and G_2 and the chlololabe cones) a difference which in the literature is supposed to be 6 3 nm I prefer to say that the difference is 5 3 THz.

I suppose that the two pigments in the cyanolabe cones are 9 13-dicis for the cyanolabe effect and the all trans form for the porphyrolabe effect, in connection with the hexagon types 2 and 1 respectively

The bond which occurs between opsin and retinene is an imine bond between lysine (or arginine) in the opsin and the aldehyde in the retinene and two (three for the 9 13-dicis form) ionic bonds with the SH or S groups in the opsin

6 The many different colour vision properties

According to my picture of the colour vision region in the X-chromosome with its three cistrons I have calculated in Part II that I expect there to be 80 dif ferent genotypes in males (3240 for females) Making this less complicated we can say that we have 16 (or possibly only 9) different genotypes for males with normal colour vision and 16 (or possibly 12) genotypes for males with defective colour vision

To see if we can distinguish between these types and find an indication of their frequencies in the population I have tested 166 male students Among the 142 males with normal colour vision the diagnoses were 71 G_1 (G_1g_{-}) 42 G_m (G_1G_2) and 29 G_2 (g_1G_{-}) These figures were not in accordance with calcula tions on the basis of the supposition of a crossing-over occurring in thousands and millions of years in females with the heterozygotic genotype G_1g_2/g_1G_2 (producing X-chromosomes with G_1G_2 and g_1g_2) By excluding the cases B_m (see Table 3 pg 23) where this property complicates the determination of the types due to the ambiguous points of pure colours we have 50 G_1 29 G_m and 24 G_2 I propose then the hypothesis that g_1 dominates over g whereby a (weak?) G_1 type is the result of the g_1g gene complex Obviously the three figures 50 29 and 24 could be an occasional example of the real expectation 25 G_1g_2 +25 g_1g_{-} 25 G_1G and 25 g_1g_{-} I found in fact these four groups with equal frequen cies when making the first calculation of the crossing-over phenomenon We have here the usually accepted relative frequencies of the phenotypes G_1 and G_2 2 1

In addition a question has been studied How can it be that deuteranomaly is more frequent (5 per cent) than protanomaly (1 per cent) although G_1 the basis for the protan series is supposed to be more frequent than G_2 the basis for the deutan series? The solution I have found by the discovery of a new type of protanomaly which has such a small deviation from normality that the observer will have a Rayleigh equation within the boundary line of normal variation, and read Ishihara as a normal but he will also read some of the tables in the colour blind way and his yellow point will lie at shorter wavelengths than normal In Table 4 pg 23) we see that the protan series is 7 + 2 + 0 + 0 and the deutan series is 7 + 3 + 1 + 1 Observing that we above have just seen that the real protan and deutan series that is the G_1 and G_2 groups possibly have an equal frequency we find that we here have solved the old problem of the frequency of deuteranomaly being greater than that for protanomaly

7 The problem of the protan deutan crossing over

According to the author s opinion the protan and deutan series are based on the properties and genes G_1 and G_2 As these two genes are assumed to be localized in one cistron a demonstrated crossing over between protan and deutan should be intra-cistronic and such an event must be supposed to be very infrequent This is not in agreement with what I have found in the literature Six families with eight cases of crossing over that is even two brothers in each of two families In Part III I have therefore studied these families The result is that only one of the cases can be explained as a crossing-over between G_1 and G_2 The other cases are shown to be a result of crossing over between the G cistron and the r_1–r_4 cistron that is inter cistronic Three of the cases the two brothers in one family and one of the two brothers in the other family (all three having been described as normal by the authors) are diagnosed by me as mesanomal *(G_1G_2 r_1 or G_1G r_2) i e will usually react as normal both in Ishihara and in the* anomaloscope

REFERENCES

Adam A The linkage between protan and deutan loci The Am J Hum Genet 22 891 1970

Akhtar M & D C Wilson Reaction mechanisms – Part (iii) Enzyme mechanisms Annual Reports on the Progress of Chemistry, Vol 68 Sect B 167–186, 1971 (Chem Soc Lond)

Arias S & A Rodriguez New Families One with Two Recombinants for Estimation of Recombination between the Deutan and Protan Loci Humangenetik 14 264–368 1972

— An Informative Large Pedigree with four compound Hemizygotes of three Combinations of Deutan and Protan Genes Acta Cient Venezolana 24 44–52, 1973a

— Description of three different phenotypes for compound hemizygotes in various combinations of deutan alleles with an identical gene of the protan locus Biol INDIO (Ven) 1 97–118 1973b

Bridges C D B The grouping of visual pigments about preferred positions in the spectrum Vision Research 5 223–238 1965

Dartnall H J A The Colour Visual Pigments Methuen London 1957

— & J N Lythgoe The distribution of visual pigments in fishes Abstr Fourth Internat Photobiol Congr Oxf Engl 1964

Fraser G R. Estimation of the recombination fraction between the protan and deutan loci Am J Human Genet 21 593–599 1969

Granit R. Sensory mechanisms of the retina Lond Oxf Univ Press 1947

Jaeger W Gibt es Kombinationsformen der verschiedenen Typen angeborener Farbensinnstorungen? Graefe s Arch. Ophthalm 151 229–248 1951

Kalmus H Distance and sequence of the loci for protan and deutan defects and for glucose 6-phosphate dehydrogenase deficiency Nature 194 215 1962

Marks W B Difference spectra of the visual pigments in single goldfish cones. (Thesis) John Hopkins Univ Baltimore 1963
— W H Dobelle & E F MacNichol jr Visual pigments of single primate cones Science 141 1181–1182 1964
Monod, J. Le hasard et la nécessité Essay sur la philosophie naturelle de la biologie moderne Edition du Seuil 1970
Pauling L. The nature of the chemical bond. Ithaca New York. Cornell University Press. 1945
Pickford R. W Compound hemizygotes for red green colour vision defects Vision Research 2, 245–252, 1962
— & R. Lakowski The Pickford Nicolson Anomaloscope Brit. J physiol Optics 17 131–150 1960
Porter I H., J Schultze & V A. McKusick Linkage between glucose-6-phosphate dehydrogenase deficiency and colour blindness Nature 193 506 1962
Richards W., Differences between color normals J optic. soc. Amer 57 1047–1055 1967
Rodriguez, A & S Arias Estimacion de la frecuencia de los Genes de Discromatopsia en un aislado etnico con el uso del Anomaloscopio de Pickford Nicolson Acta Cient. Venezolana 22 199–206 1971
Rubin, M L. Spectral hue loci of normal and anomalous trichromates Amer J Ophth. 52 166–172 1961
Rushton, W A H Blue light and the regeneration of human rhodopsin in situ. J gen. Physiol. 41 419–428 1957
— Kinetics of cone pigments measured objectively on the living human fovea. Ann. N Y Acad. Sci 74 291 304 1958
— Visual pigments in man Scientific American 207 120–132 1962.
Siniscalco M., G Filippi & B Latte Recombination between protan and deutan genes data on their relative position in respect of the G6PD locus. Nature 204 1062–1064 1964
Thuline H C W E. Hodgin G R. Fraser & A. C Motulsky *Genetics of protan and deutan anomalies An instructive family* Am J Human Genet. 21 581–592, 1969
Vanderdonck R. & G Verriest Femme protanomal et hétérozygote mixte Biotypologie 21 110–120 1960
Waaler G H M. Über die Erblichkeitsverhältnisse der verschiedenen Arten von angeborener Rotgrünblindheit Z. f indukt Abst u. Vererb lehre 45 279–333 1927
— The heredity of normal and defective colour vision. Avh. d. Norske Vidensk. Akad I No 9 3–25 1967
— New facts in genetics of colour vision besides ideas of the colour perception Ibid No 11 3–24 1968
— Studies in colour vision Ibid. No 12 3–32, 1969
— Further investigations on different hereditary colour vision properties Ibid. No 14 3–13 1973a.
— *Genetics and physiology of colour vision Acta ophthalmologica Suppl. 122* 5–75 1973b
Wald G Vitamin A in eye tissues J gen. physiol 18 905–915 1935a.
— Carotenoids and the visual cycle J gen physiol. 19 351–371 1935b
— Pigments of the retina. J gen physiol 20 45–56 1936

— Visual purple system in fresh water fishes Nature 139 1017–1018 1937
— The metamorphosis of visual systems in the sealamprey J gen physiol. 40 901–914 1957
— The photoreceptors in vision Chapter XXVIII in Handbook in Physiology Wash D C. 1959
— P K. Brown & H Smith Cyanopsin a new pigment of cone vision Science 118 505–508 1953
— P K. Brown & H Smith Iodopsin J gen physiol 38 625–681 1955

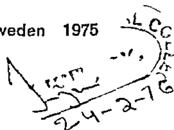
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OFFICIAL TRANSACTIONS

Edited by H Bynke M D

Examination methods

A Oksala The benefits and limits of ultrasound diagnosis in ophthalmology 5

H Fledelius Diagnostic ultrasound in orbital diseases 6

S E Nilsson and K -O Skoog The directly recorded standing potential of the human eye and its long-term variations in response to changes in illumination 8

C E T Krakau and R Ohman An apparatus for ERG recording adaptable to the slit lamp microscope 9

E Schyberg Fine needle biopsy of orbital tumours 11

E Linnér and H Wallman Low light level television system to estimate retinal blood flow by fluorescein angiography 11

U Axelsson A new instrument for the radioactive phosphorous uptake test 12

I Hørven Corneal temperature registrations in temporal arteritis and CRA-embolism 13

M Davanger Description and demonstration of a new exophthalmometer 15

A Palkama K Kalliomaki and P Miettinen An electronic device for pupillary measurement 16

K Viikari The polyphasic fogging method for revealing spasm of accommodation 17

Visual fields

E Godtfredsen Bilateral homonymous hemianopsia 20

E Hansen Static perimetry during chromatic adaptation The method applied for investigation of amblyopia 21

A Heijl and C E T Krakau An automatic perimeter 23

H Bynke and A Heijl A portable hemianopsia tester 24

O Holm Visual field widening in retinitis pigmentosa 25

Retina and optic nerve

A Vannas and C Raitta Photography of the nerve fiber layer in retinal disturbances 27

C Raitta and U Karhunen Fluorescein angiography in general anaesthesia - technique and indications 27

J Sjostrand J -O Karlsson and W G McLean The effect of chloroquine on the retina and the nervous system 2)

B Ehinger Interplexiform cells A recently discovered retinal main cell type 30

B Lindberg-Bauer Light evoked release of glycine from rabbit retina 30

Glaucoma and ocular hydrodynamics

N Ehlers and T Bramsen Importance of corneal thickness in applanation tonometry 32

P Nelleman Sørensen The AO - non contact tonometer 32

T Jerndal Gonioscopic findings of importance for classification of glaucoma 33

M Pandolfi Factor VIII in aqueous outflow pathways 34

T Bramsen Amyl nitrite test in glaucoma simplex 35

O Nissen Acetazolamide used diagnostically on suspicion of disease in the circulation of the aqueous humour Comparison with weight tonography (preliminary results) 36

R Ralli Clonidin effect on the intraocular pressure and eye circulation 37

A Palkama A Koivo and J Stjernschantz Direct fluorometric measurement of aqueous humour flow 38

J Stjernschantz and A Palkama Aspects of the influence of parasympathetic stimulation on aqueous humour dynamics in the rabbit 38

K Wilke Episcleral venous pressure and pregnancy 40

Tear-film and cornea

M S Norn Wetting time 42

T Sørensen Determination of tear flow using a radioactive tracer 43

S Vannas K Karjalainen P Ruusuvaara and A Tiilikainen Prophylaxis of allograft reaction in corneal grafting 44

T Bertelsen and V Seim Irreversible mydriasis following keratoplasty in keratoconus 45

P Rysa and J Sarvaranta Simultaneous thermal recording of corneal temperature and blinking frequency in simulated arctic conditions 46

J U Prause A semiquantitative enzyme assay for corneal collagenase 46

A Huhtala T Tervo and A Palkama Automatic and somatic sensory nerves of the iris and cornea 47

Lens and uvea

B Philipson and P Fagerholm Opacification at traumatic cataract 49

M Palva and A Palkama Effect of X-ray irradiation on the ultrastructure of the lens epithelium and its sodium-potassium activated adenosine triphosphatase (Na-K-ATPase) activity 50

M Saari and R Miettinen Evaluation of diagnostic tests based on uveitis survey at the Oulu University Eye Hospital 51

A Karma and S Sutinen Conjunctival biopsy in sarcoidosis 52

A M Tønjum Movement of horseradish peroxidase in the anterior parts of the eye 54

O Ø Pedersen Electron microscopic studies on the effects of prostaglandins on the blood-aqueous barrier of the rabbit eye 55

E Bengtsson The aqueous flare inducing effect of prostaglandin and α-Melanocyte stimulating hormone 55

General Meeting 58

The benefits and limits of ultrasound diagnosis in ophthalmology

By

A Oksala

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The ultrasound technique in its present form has been used in the diagnosis of eye diseases for some twenty years With the improvement in the equipment and with the great increase in both theoretical research and practical experience we now know more about the present possibilities and limits of ultrasound diagnostic methods

In the diagnosis of diseases of the orbit the eyelids and the lacrimal ducts ultrasound methods are chiefly used to distinguish the liquid-filled cavity from solid tissue Ultrasound examination allows us for example to differentiate clearly between an abscess a mucocele and a dermoid cyst on the one hand and a tumour on the other Histologically quite different tumours can also acoustically be differentiated from each other

In cases of scleritis the tissue may become many times thicker than normally and the measurement of this thickness is relatively easy using the ultrasound technique The extensive thickening of the sclera may be considered one of the most important objective findings in cases of scleritis posterior

In recent years I have used ultrasonic examination more and more in planning the treatment of certain diseases and in estimating the effect of treatment this has been true chiefly in the case of diseases involving clouding of the vitreous body In cases of acute and chronic iritis the optical examination of the vitreous body may be difficult owing to the clouding of the aqueous fluid or to pupillary seclusion or occlusion If exudation into the vitreous body is considerable the optical examination of its deeper part becomes difficult or impossible Such exudation extensively reflects low and moving echoes and the use of the ultrasound technique enables us to follow the effect of treatment on the extent and location of exudation

Since uveal melanoma usually necessitates treatment as radical as enucleation all possible examination techniques should be used in diagnosis So far I have examined approx eighty cases of uveal melanoma by means of ultrasound and in all cases echogrammes characteristic of the disease have been obtained In cases of glaucoma absolutum some 10 % of which are accompained by melanoma the use of ultrasound to exclude the possibility of the latter gives great certainty and thus eliminates needless enucleation

Ultrasound examination can be used both to detect and to localize detachment of the choroid A detached choroid of at least 1 mm in height may be detected by ultrasound examination In my examinations of cases of idiopathic detachment of the

retina in some 15-20 % of cases I have observed by ultrasound a low detachment of the choroid

Optical examination of the posterior part of the vitreous body is clearly more difficult than that of the anterior due in great part to the fact that the reflexes from the optic fundus weaken the contrasts In such cases ultrasound examination yields valuable additional information also concerning a clear vitreous body

One of the most grateful objects for the use of ultrasound in diagnosis is that of idiopathic detachment of the retina Such detachment can be detected and localized by ultrasound if its height is at least 1 mm For differential diagnosis by ultrasound alone however a height of at least 2 mm is needed

In secondary detachment of the retina the exudation in the subretinal fluid reflects low mobile echoes If there is coagulated blood beneath the detached retina it reflects high immobile echoes and it is difficult to distinguish it by ultrasound from melanoma Uncoagulated blood under the retina however reflects rather high mobile echoes

In cases of contusion in which an extensive hyphaema is present the deeper part of the eye can be examined only by means of ultrasound In cases of perforation of the eye which usually involves clouding of the lens the condition of the posterior parts of the eye can likewise be ascertained only ultrasonically All foreign bodies penetrating the eye including those which are X-ray negative can be detected and localized by means of ultrasound provided they have a diameter of at least 0 05 mm Accuracy of localization is almost equal with both the A and the B-scan method In the anterior part of the eye the possible error is of the magnitude of 1-2 mm and in the posterior part approx 2-4 mm

Ultrasonic examination can be of great benefit in the localization of foreign bodies close to the fundus of the eye in particular when we wish to ascertain whether the particle is within the eye or not The assumption in X-ray examination is that the diameter of the eye is 24 mm If the true diameter deviates from this the X-ray localization will give a faulty result which can be corrected only by measuring the real diameter of the eye by means of ultrasound

Diagnostic Ultrasound in Orbital Diseases

By

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Until 1972 less than two per cent of the ultrasonographies performed in the Copenhagen Eye Clinic of Rigshospitalet concerned orbital disease (Fledelius 1973) Recently however an increasing number has been referred and the present (abbre-

viated) report deals with our experience from a series of 46 non thyroid orbital cases

Time-amplitude ultrasonography (A-scan) was performed with a Kretztechnik 7000 equipment and a plane 8 Mc transducer A tumoursensitivity setting (Ossoinig 1973) was aimed at Transbulbar as well as extrabulbar echograms from the two sides were compared in symmetrical sound beam directions Prolonged echo-trains of the diseased side indicated the presence of a pathological lesion within the orbit The positive findings were divided into cystic and solid patterns among the latter rather typical echograms were recognized from cavernous haemangiomas

Table I Orbital ultrasonography (A-scan) in 46 patients

A 31 verified cases (microscopy and/or clinic)
- 19 after surgery
- 8 foreign bodies
- 2 carotico-cavernous aneurysms
- 2 *pseudo-proptosis (unilateral high myopia)*

B 15 tentative cases
- 7 echo positive (three presumed vascular lesions one mucocele three obs)
- 8 echo-negative

Table I shows the division of the series into so-called verified cases (by microscopy or unambiguous clinical history/findings) and the cases with only tentative diagnoses Among the histopathologically proven were three infants in which early recurrence of embryonal sarcoma was demonstrated with ultrasound Two of the foreign body cases dealt with pieces of glass undetectable by ordinary X-ray-examination Measurement of the ocular axial lengths clarified the true nature of the two cases of pseudo-proptosis

In the 15 tentative cases the clinical course and findings did not lead to surgery or other definite confirmation Among the seven echo positive ca es was a patient with an orbital varix which filled dramatically after a Valsalva-maneuver within 10-15 seconds a mostly cystic pattern emerged on the oscilloscope Eight cases were considered echo negative

The non-verified cases impede a full analysis as to the correctness of the ultrasonic findings in the whole series We may state however that no false positive echopatterns occurred On the contrary there were five false negatives they comprised two pseudotumours (one with earlier biopsy one demonstrated by computer assisted tomography) and three foreign body cases

Due to the rather limited experience (plus suboptimal equipment ?) we have not been able to compete with the high level of diagnostic reliability recently reported by Ossoinig (1975) and this applies to the field of tissue differentiation as well Yet we feel justified to consider ultrasonography a valuable diagnostic supplement to other examination procedures of the orbit In our experience ultrasound has proven especially useful for the determination of the optimum site for biopsy which we still consider the conditio sine qua non for correct treatment in most cases of orbital disease

The size of the present series finally stresses another point the relatively rare occurrence of orbital tumours Therefore a centralization of such cases would undoubtedly improve diagnostic as well as therapeutic results

References

Fledelius H (1973) Ugeskrift Laeg 135 1888-1890

Ossoinig K (1973) In Massin & Poujol ed Diagnostica Ultrasonica in Ophthalmologia pp 131-137 Paris

Ossoinig K and Till P (1975) In Ultrasonography in Ophthalmology Bibl Ophthal 83 p 200-216 Karger Basel

The directly recorded standing potential of the human eye and its long-term variations in response to changes in illumination

By

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Earlier the standing potential (SP) of the human eye has been studied only indirectly using the electrooculogram (EOG) By means of a newly developed method including a suction contact lens for the eye and a reference chamber for the forehead connected by saline - agar bridges to matched and temperature stabilized calomel half-cells serving as recording and reference electrodes d c amplification and averaging technique stable and reproducible long-term direct registrations of the SP could be obtained Sudden changes in illumination of the eye caused characteristic cyclic variations of the SP

An alteration from darkness to 16 Lux provoked a rather fast transient negative change of the SP (maximum amplitude after 0 5-1 min) followed by much slower variations (frequency about 2/hour) in the form of damped oscillations the first one of which started in a positive direction The maximum amplitude of this first slow oscillation was about 5 mV When instead the illumination was changed from light to darkness the polarity of the oscillations was reversed and the amplitude was smaller As to frequencies and phases the results correspond well to the findings obtained in indirect EOG measurements

We have demonstrated earlier that also the amplitude of the slow c-wave of the electroretinogram (ERG) when repeatedly recorded varies in the form of damped oscillations with a frequency of about 2/hour With the present techniques allowing simultaneous recordings of the SP and the c-wave it could be shown that the variations of these two potentials were parallel This finding can be explained by the fact that the SP and the c-wave are known to have part of their origin in common in the pigment epithelium The two potentials ought to be of interest as a reflection of the function of the pigment epithelium under various conditions e g after the influence of drugs

An apparatus for ERG recording adaptable to the slit lamp microscope

By

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With the aim of simplifying the clinical ERG recording an instrument adaptable to a slit lamp microscope was constructed Like the applanation tonometer a perspex body is balanced so that when released it approaches the patient s cornea (Fig 1) The adjustment is facilitated by using a low magnification of the microscope The end of the perspex body has a ring-shaped Ag-Ag Cl electrode and centrally there is mounted a light emitting diode (LED) which serves as a stimulation light During operation contact between electrode and cornea is formed by a drop of methylcellulose (2 per cent) containing NaCl An indifferent electrode is placed on the forehead The stimulation light is activated as single pulses by pressing a button or flashes automatically at a variable impulse frequency The LEDs are easily modulated so that the height and the intensity of the light pulse are variable The ERG response may be mixed with random noise AC from the mains etc and it is often necessary to improve the signal noise ratio This has been achieved by using the following devices

a) a device which adjusts the potential to a zero level each time the stimulus light is flashed The recording thus starts at the same level after every flash (Fig 2) This device reduces the range inside which the signal is found

b) an averager which superposes an arbitrary number of recordings on each other and calculates the mean curve The average curve and the last recording are simultaneously shown on the oscilloscope screen The averaged curve can after an arbitrary number of superposed sweeps be recorded by an ink writer

The amplifiers are DC coupled which permits the recording of the C-wave The frequency response is constant in the range 0 to 250 Hz The first step is a differential isolation amplifier (Analog Devices 273 K) The patient is grounded by a hand-held electrode but no Faraday cage is needed

LEDs are manufactured in different colours (red green yellow) and the light source can easily be changed to any of these colours The half-width of the wave length distribution is about 400 Å for each colour

The set up is compact and seems suitable for clinical work A routine ERG on both eyes may be obtained - apart from the eventual period of dark adaptation within 5 to 10 min

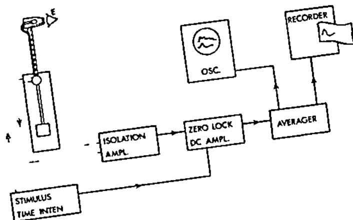


Fig 1

Block diagram of the ERG apparatus
I electrode placed on the forehead
E patient s eye

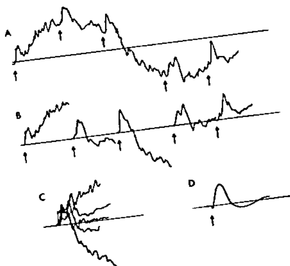


Fig 2

A crude recording
B recording after zero adjustment at flashing
C superposition of a number of sweeps
D the averaged curve
Flashes at the arrows

Fine needle biopsy of orbital tumours

By

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The diagnosis of tumours causing unilateral exophthalmos is often difficult We have seen seventeen cases of unilateral exophthalmos in the last two years and in eight of these an orbital tumour seemed highly probable The suspected tumours were localized with ultrasound carotid angiography phlebography and scintigraphy In all eight cases a tumour diagnosis could be established by fine needle biopsy and cytological examination No local anaesthesia was necessary The ophthalmologist made the puncture of the tumour and the cytologist then made the aspiration and prepared the slides So far we have seen no complications of this technique which is easily performed and causes the patient little or no discomfort The risk of spreading of the tumour seems to be very small

Low light level television system to estimate blood flow by fluorescein angiography

By

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The fluorescein angiography technique developed by Novotny and Alvis (1961) has been of great clinical importance Several attempts have been made to improve this method

According to van Heuven et al and Yuhasz et al (2 6) it has been possible to record a fluorescein angiogram with low light television Attempts have been made by others to measure blood flow transit times (1 3 5) These results cannot be used to calculate the blood flow rate since data on the volume of the vascular system are not available

To the best of our knowledge there is no technique available for measurements in the clinic of human retinal blood flow The purpose of the present project is to develop a method for a quantitative estimation of this blood flow based on fluorescein angiography and television With this method a continuous fundus image with sufficient resolution is projected on the television screen This allows observations

at light levels lower than those used with regular photographic technique and below light intensities that could be harmful to the eye The principle of this method is to follow on the television screen the movement of the blood-fluorescein border line in the arterioles close to the disc during the earliest arterial phase This movement can be measured during very short periods of time

The cross-section of the vessels is assumed to be related to the volume of the vessel so that it can be used as an approximate volume-index This assumption has been used in preliminary investigations of the cross-section of retinal blood vessels (3) It is clear that the parts of the vessels that contains fluorescein do not reflect directly the total blood volume but it seems possible to conduct this to the blood volume flow in such a way that a useful estimation can be made

The development of a low light level television technique with a sufficient resolution contains several problems This work shall be carried out in close cooperation between the departments of medical electronics and ophthalmology

References

Hart L M Heyman A Linhart J W McIntosh H and Davies N J (1963) Fluorescein motion picture photography of retinal circulation J Lab Clin Med 62 703

van Heuven W A J Schaffer Ch A and Mehu M The use of low light level television in fundus imaging Photography in Ophthalmology Int Symp Fluorescein Angiography Miami Fla 1970 Mod Probl Ophthal 9 9-16 Karger Basel 1971

Hickam J B and Frayser R (1966) Studies of the retinal circulation in man Observations on vessel diameter arterio-venous oxygen difference and mean circulation time Circulation 33 302

Linnér E (1972) Point sampling technique for quantitative analysis of the retinal circulation in the intact human eye Transactions of the Swedish Ophthalmological Society Meeting in Stockholm Nov 27 1971 Acta Ophthal (Kbh) 50 629-630

Oberhoff P Evans P Y and Delaney J F (1965) Cinematographic documentation of retinal circulation times Arch Ophthal 74 77

Yuhasz Z Akashi R H (1973) A new apparatus for video tape recording of fluorescein angiograms Arch Ophthal 90 481-484

A new instrument for the radioactive phosphorous uptake test

By

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The radioactive phosphorous uptake test (the P^{32} test) for differentiating benign from malignant growths within the eye has been in clinical use for more than two

decades However the results have not always been reliable above all not in eyes with posterior lesions One reason is that the probes used have been rather thick and therefore difficult to place properly over the suspect lesion without broad surgical exploration of the posterior part of the globe

In an attempt to develop a probe allowing measurements under ophthalmoscopic control a modification has been made of the so-called needle detectors constructed by AB Atomenergi Studsvik Sweden A tubular probe with an outer diameter of 2 2 mm is bent to a 60° angle about 15 mm from its distal end where it contains a small 2 x 5 mm silicone element On the concave side of the probe at the distal end of the silicone element is a cone-shaped tip 0 7 mm in height With this construction the probe can be used like a Meyer-Schwickerath indicator and under ophthalmoscopic control can be accurately placed over the lesion to be examined

The detector has been tested on 7 eyes with histologically verified malignant melanomas of the choroid Measurements were done 48 hours after intravenous injection of P^{32} (10 µC/kg body weight maximum dose 750 µC) Uptake over the tumour ranged from 130-290 % in good agreement with results reported by other investigators using other types of probes However a small malignant melanoma of the ciliary body showed no increased uptake of P^{32}

Corneal temperature registrations in temporal arteritis and CRA-embolism

By

I Hørven

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A thermistor probe for direct corneal temperature registration has been designed The normal range of corneal temperatures is between +32 0 and +33 0 °C with only negligible differences between the two eyes It is well known that choroidal blood flow is extensive compared with other tissues of the body The arterial blood comes pre-heated to the eye from the warm thorax cavity Alterations in ocular blood flow has been shown to induce a corresponding alteration in the ocular temperature (Bill 1962) In accord with this Colle et al (1931) showed that internal carotid artery occlusion in cats and dogs induced a marked drop in ocular temperature Braendstrup (1952) demonstrated increased corneal temperature in anterior eye inflammations and haemorrhagic glaucoma

The present study consists of three groups of patients and the results are given in the table

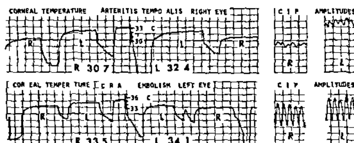
Corneal temperature in + °C

	No	Right eye Sympt side	Left eye Asympt side	Diff	Sign x)
Polymyalgia rheumatica (no eye involvement)	7	32 13	32 04	+0 09	-
Temporal arteritis xx) (3 unilateral 4 bilateral)	7	31 97	32 87	-0 90	t=3 154 P 0 02
CRA-embolism	8	32 94	32 69	+0 25	t=2 376 P 0 05

x) Statistical method of paired comparison

xx) In bilateral ca es the coldest eye is listed first

The five fresh cases of temporal arteritis demonstrated large side differences while the two old cases which had received steroid treatment for years demonstrated no side difference suggesting that the ocular blood supply in these two patients was now normalized In CRA-embolism the slight but significant increase in temperature on the affected side may point to a choroidal hyperemia probably initiated by and compensating for the retinal hypoxia caused by the CRA-embolism Typical results from two patients are shown in the figure



Decrease in corneal temperature in a patient with temporal arteritis increase in corneal temperature in a patient with central retinal artery (CRA) - embolism (CIP - amplitudes = corneal indentation pulse amplitudes)

In accord with the above results corneal temperature registration is introduced as a diagnostic tool for distinction between temporal arteritis and CRA-embolism in addition to the well-established methods such as dynamic tonometry (Hørven 1973) ESR ophthalmoscopy and temporal artery biopsy

References

Bill A (1962) Intraocular pressure and blood flow through the uvea Arch Ophthal 67 336-348

Braendstrup J M (1952) Øjets kliniske temperatur Dansk Videnskabs Forlag A/S København pp 99

Colle J Duke-Elder P M and Duke-Elder W S (1931) Studies on the intraocular pressure Part I The action of drugs on the vascular and muscular factors controlling intraocular pressure J Physiol 71 1-30
Hørven I (1973) Dynamic tonometry V Further studies of the corneal indentation pulse in temporal arteritis Acta Ophthal (Kbh) 51 353-366

Description and demonstration of a new exophthalmometer

By

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The purpose of exophthalmometry is to measure the distance between apex corneae and a frontal plane through the deepest point on the lateral orbital margin on both sides This distance can not be measured directly Instead apex corneae is projected against a millimeter scale placed horizontally in a sagital plane through the lateral orbital margin A correct result depends on correct solutions to the following problems

1 The zero point of the scale must be placed correctly on the lateral orbital margin

2 The scale should not deviate from a sagital plane

3 Apex cornea must be projected against the scale at a right angle

4 The position of the projection of apex corneae against the scale should be read accurately

None of the exophthalmometers in general use yields a good solution to all these problems (Davanger 1970)

A new exophthalmometer is constructed in which measuring errors caused by incomplete solutions to those problems in principle are eliminated

A millimeter scale is placed in the sagital plane through the lateral orbital margin on both sides simultaneously so that deviation from the sagital plane is avoided The footplate to be placed against the orbital margin is straight and in a frontal plane whereby minor lateral displacement does not result in the zero point of the scale being removed from the correct position

A right-angled prism can be slided along the scale Vertical lines are drawn on the two sides which are adjacent to the right angle By looking exactly along a sagital plane the examiner can bring the two lines to coincide The line of vision is reflected 90^{o} by the prism hypotenuse and consequently proceeds towards the profile of cornea along a frontal plane

By sliding the prism along the scale the coinciding lines can be brought to be a tangent to apex corneae Now the position of one of the vertical lines on the prism along the millimeter scale indicates the exophthalmometric value

Practical measurements with an exophthalmometer constructed according to these principles demonstrated that more reproducable results were obtained with this instrument than with those in general use

An improved version better suited for serial production was designed by M Szalay It is composed of commercial available caliper rules One caliper rule is held in a frontal plane and can be adjusted to the interorbital distance of the patient Two caliper rules is placed at a right angle to the first and with their zero points on the lateral orbital margin on each side The prism is fixed to the sliding branch of these caliper rules and can be brought to its position by moving a gear-wheel along a cog-rod with the index finger

The measurement takes place in two steps First the prism slides are brought to the right positions and then the result is read with an accuracy of 1/10 mm by the help of a vernier

The critical part of the measurement namely the adjusting of the prism slides is performed without the examiner seeing the scales Then the knowledge of previous results does not influence and several independent measurements may be performed Thereby the accuracy may be increased by calculating the average of series of independent measurements Also the statistical significance of average values differing from one examination to the next may be calculated

In series of 10 consecutive measurements on the same individuals at the same time an average standard deviation of 1/3 mm was found by M Szalay and by the author This means that 68 % of the single results are in the range of the average value ± 1/3 mm This is a considerable improvement as compared with the exophthalmometers in general use Changes in the degree of exophthalmus may be demonstrated earlier and with greater reliability with this new exophthalmometer

References

Davanger M (1970) Principles and sources of error in exophthalmometry A new exophthalmometer Acta Ophthal (Kbh) 48 625-633

An electronic device for pupillary measurement

By

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In order to register the success of denervations or stimulations on various autonomic nerves of the eye an electronic device for measuring pupillary diameter was developed A comprehensive review of the litterature relating to pupillary measurements revealed that the technical basis for this instrument was based

on a concept not previously reported thus it was in itself an original research device developed in our laboratory and worthy of publication

The earlier instruments are based either on the recording the pupillary diameter on cine-film or registering the largest diameter of pupil by scanning with an electro-mechanical device (Loewenstein and Loewenfeldt 1958 Schafer 1971)

In our new instrument the eye is illuminated in a dark room by infra red light - emitting diodes (LED 6 x 6 mW) The entire iris is viewed by an infra red-sensitive vidicon camera The video-signal is fed to a TV-monitor and to an electronic line-contrast measuring device This device measures the length of one line (diameter line) in the dark pupil The current is proportional to the length of the line (equal to the pupillary diameter) and is fed into a pen recorder

The reliability of the instrument has been tested Its out-put is in linear relationship to the pupillary diameter and the error is less than 1 5 per cent

The instrument has been successfully adapted for measuring pupillary diameters under various experimental conditions It has been shown to record a linear result during both in maximal miosis and mydriasis Furthermore it should be pointed out that light reflexes of the pupil can be avoided and the measurements are performed without touching the eye The apparatus can be easily adapted as well to clinical studies

References

Loewenstein O and Loewenfeldt I E (1958) Arch Ophthal 59 352-363
Schafer W D (1971) Der dtsch ophthal Ges 661-664

The polyphasic fogging method for revealing spasm of accommodation

By

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Spasm of accommodation is a cramp resulting from the exhaustion of an overworked ciliary muscle and it will not relax without help from outside The subjective signs are headache and frequently also diminished distant vision Objective symptoms that can be seen often include one or more vertical furrows on the brow It is typical of spasm of accommodation that even with cycloplegics it cannot be completely relaxed

There are two basic events in the regulation of accommodation a partial regulation which means the crude approaching of the object looked at and a second or fine regulation which leads to the actual focusing By fogging one aims at voluntary knowing prevention of the phase of adjustment thus also preventing the exact focusing which provokes the spasm of accommodation

By means of the fogging examination the refraction error is determined subjectively It is always begun binocularly by placing in the test frames plus lenses many diopters stronger than the refraction values achieved in retinoscopy for example +7 0 With these the patient is made to look at the greatest optoptype on the chart A person who achieves a visus of 0 05 with +7 0 glasses is a hypermetrope of at least 3 5 diopters Correspondingly a visus 0 1 achieved with lenses +1 5 is evidence that the patient cannot be a myope notwithstanding the fact that he can only achieve a visus of 1 0 with lenses of for example -5 0 diopters

As a basis for actual treatment a visus of a class of magnitude of 0 3 has proved to be particularly appropriate Lenses one diopter less than those with which this is achieved are the ones with which the patient can manage in daily life

To make the patient look in different ways helps in achieving the greatest possible revelation of spasm of accommodation (= latent hypermetropia) and for this reason fogging is carried out both with the patient looking out of the window for example at car registration numbers and reading a close text

In reading glasses the aim is also the strongest possible lenses with which the patient can still manage his work Very useful additional information can also be derived from the Maddox-wing test with fogging Particularly in the case of young people corrections for near vision have received altogether to little attention It is however on just this that prevention of so-called school myopia depends By using plus glasses for reading as early as possible - either ordinary monofocals or preferably half lenses or ordinary bifocals and in spite of possible diminished distant vision - it is possible to put the brake on any further straining of the spasm of accommodation By rapidly strengthening reading glasses it is possible to make an already developed spasm of accommodation give way Plus reading glasses of three or four diopters ensure that there is no risk of the refraction situation sliding to the minus side i e to pseudo-myopia

Perhaps my most significant clinical results have been connected with migraine patients altogether approximately 1 000 cases A follow-up which was made of 100 consecutive patients from this material gave the following results

cured	56	
considerable improvement	14	
improvement	8	
		78
failed to carry out instructions/ ceased treatment	8	
no reply	14	
		22
		100

In a further group of 234 consecutive patients who with the exception of a few presbyopes who had worn reading glasses had not earlier worn glasses the use of plus lenses in treatment produced the following results

cured	106	
considerable improvement	37	
improvement	29	
		165
failed to carry out instructions/ ceased treatment	19	
no reply	50	
		69
		234

Of the fifty who did not reply many are known to me as patients who have for years been in a vicious circle of tests attempted treatment and use of drugs

The above results in the treatment of migraine are to be seen as deriving from the fogging method The fogging method also seems to show how rampant hypermetropia is and how from the point of view of general health spasm of accommodation with all its consequences plays a most significant part in upsetting the balance of the autonomic nervous system Merely by correcting hypermetropia to the greatest possible extent it is possible to achieve great therapeutic victories – not least in the case of troubles usually classified as psycho-somatic or neuro-vegetative

Unfortunately all this takes a lot of time but once it has been done the matter is arranged and the program of treatment resolved for a long time ahead The only thing to remember is that the maximum amount of hypermetropia discovered is always true

Bilateral homonymous hemianopsia

By

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Bilateral homonymous hemianopsia is a rare symptom but possibly more frequent than proposed Many of the patients are too invalidated to cooperate and paradoxically in many cases the patients are not conscious of their visual lesion The symptoms of cortical blindness are very similar to those of bilateral homonymous hemianopsia and are characterized by loss of vision normal pupillary reflexes for light and normal ophthalmoscopy The visual pathway and its anatomy including the vascular supply is shortly recapitulated Modern neuroradiologic examination especially the Seldinger aortography seems of great value to clarify the exact vascular pattern The etiology of bitemporal homonymous hemianopsia is 1) traumatic blunt or penetrating cranio-cerebral lesions or 2) of vascular sclerotic nature

The incidence of homonymous hemianopsia in comprehensive materials (Lawton Smith 1962) shows that most of the cases (approx 75 per cent) are localized in the occipital and parietal lobes

From a large material of strokes (Marquardsen 1969) it appears that only two per cent of the cases exhibit homonymous hemianopsia the figures for bilateral homonymous hemianopsia are not given in that study

From own experience based on twenty years neuro-ophthalmologic practice some cases are reviewed commented and illustrated by X-radiographs The cases demonstrate the development unilateral as well as bilateral resulting in crossed or altitudinal hemianopsia (Enoksson 1965)

The blunt cranio-cerebral concussion with cortical blindness is rare less than one per cent as shown in a great neuro-surgical material collected during 14 years in Copenhagen (Gjerris and Mellemgaard 1969) Children were overrepresented the prognosis was good

In vascular ischaemic arteriosclerotic cases the prognosis is bad Therapeutic possibilities are few reconstructive vascular surgery seems of limited value (Hutchinson and Acheson 1975)

References

Enoksson P (1965) Perimetry in neuro-ophthalmological diagnosis Suppl 82 Acta Ophthal (Kbh) pp 54

Gjerris F and Mellemgaard L (1969) Transitory blindness in head injury Acta Neurol Sc 45 623-631

Godtfredsen E (1970) Neuro-ophthalmological focal diagnosis Acta Ophthal (Kbh) 48 667-671
Hutchinson E C and Acheson E J (1975) Strokes natural history pathology and surgical treatment pp 283 Saunders London
Lawton Smith J (1962) Homonymous hemianopsia Amer J Ophthal 54 616
Marquardsen J (1969 The natural history of acute cerebrovascular disease Dissertation pp 192 Munksgaard Copenhagen
Symonds C and Mackenzie I (1957) Bilateral loss of vision from cerebral infarction Brain 80 415-455

Static perimetry during chromatic adaptation The method applied for investigation of amblyopia

By

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When examining eye diseases which entail cone affections there is a want of clinical methods which could differentiate between the individual cone mechanisms Applying a method which is based upon the STILE s two-colour-threshold-technique such a differentiation can be obtained with the static perimetry being performed during chromatic adaptation (Hansen 1974) This investigation is carried out on amblyopic patients using the same method which has been improved

The red receptor mechanism is registered during adaptation to a blue background (obtained with Wratten filter no 47) and the green sensitive mechanism while adapting to a purple light (Wratten no 34A) For registration of the blue receptor mechanism a monochromatic yellow at λ=589 nm from a low pressure Na-lamp is used The lamp is mounted across the upper part of the perimeter The light is reflected by a shade giving a diffuse illumination of the sphere With interference filters attached to the projection arm the object light is made nearly monochromatic (the half-band width of the filters being about 12 nm and their maximal transmission about 30 %) Object lights at λ=583 nm λ=552 nm and λ=451 nm are selected for static perimetry in the blue purple and yellow lights respectively A halogen lamp of 6 V 20 W is used Instruments for regulation and control ensure constant conditions of examination

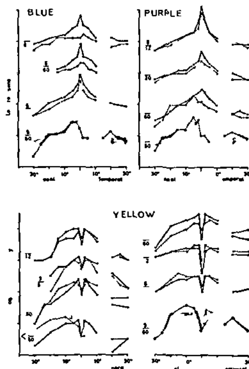
11 patients between 10 and 59 years were examined 6 had strabismic amblyopia and 5 anisometropic amblyopia Eccentric fixation was recorded in 4 the remaining patients had central fixation Except for 1 patient all had normal vision in their best eye The colour vision was normal

The perimetric profiles show a central depression in the amblyopic eye when the red sensitive cones as well as the green sensitive cones are concerned The depression is more pronounced the higher the degree of amblyopia In general the blue sen-

sitive mechanism shows no corresponding depression Characteristic of the blue receptor curve is a central dip which is on an average less pronounced in the amblyopic eye than in the good eye In 6 patients fixating centrally no significant difference of threshold values was found between the amblyopic and the good eye throughout the perimeter curve except for the fixation point where the sensitivity was significantly better for the amblyopic eye ($P < 0\ 05$)

By registration of the blue receptor curve a distinct age factor is observed In the younger patients (aged 10-24 years) the sensitivity level was generally higher than in the older patients (aged 26-42 years) The difference here is evidently related to the age differences of the transmission of blue light in the ocular media

In our cases with eccentric fixation the true fovea represents the relatively best sensitivity of the red as well as of the green receptor mechanism



Static perimetry in the two eyes during adaptation to the background colours The dark lines indicate the good eye and the dotted lines the amblyopic eye Object size IV (16 mm^2)

References

Hansen E (1974) The colour receptors studied by increment threshold measurements during chromatic adaptation in the Goldmann perimeter Acta Ophthal (Kbh) 52 490-500

An automatic perimeter

By

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The majority of visual field investigations in clinical practice concern glaucoma patients or glaucoma suspects An automatic device for dealing with this group might be of considerable help in clinical work

Such an apparatus capable of testing the central visual field statically has been constructed

The patient is placed in front of a board with a central red fixation light and with a background illumination of 1 cd/m^2 In the board of light-emitting diodes are mounted in circular patterns at 5 10 and 15^0 eccentricity There are eight further lights outside these circles The LEDs can be lit at 16 intensity levels the ratio between the intensities of two consecutive levels being 1 2

The perimeter is interfaced with a minicomputer (Nova 1200) which receives orders from the patient via a push-button and determines which test light is to be lit and at what intensity level The patient is instructed Press the button when you see a light The test logic containing the rules according to which the visual field is tested is stored in the memory of the computer At the end of the session a polar diagram of the test result is produced (Fig 1) Using the present logic the time required for testing one eye is 10-12 min

In 21 eyes - 12 with undoubted field defects - tested with this perimeter and checked by kinetic Goldmann perimetry and mostly also by static profile perimetry no single visual field defect was missed by the automatic perimeter Usually a good correspondence existed between the location of the defect by conventional and by automatic perimetry In some cases however mostly pilocarpine-treated glaucomatous eyes automatic perimetry indicated larger defects than those obtained by conventional methods The material is too small to admit of a consistent estimate of the frequency of false positives when using this method

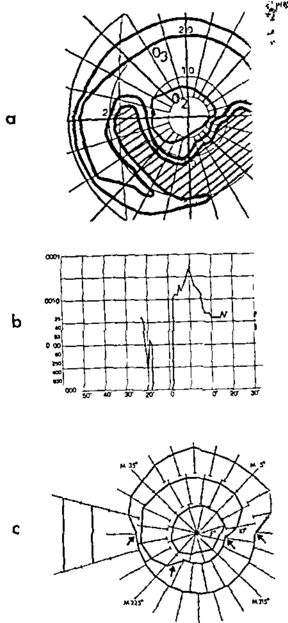


Fig. 1 Visual field in a glaucoma patient (left eye)
a Kinetic Goldmann perimetry (central field)
b Static profile (45° meridian)
c Automatic perimetry There is one scale for each of
Low sensitivity is plotted nearer origo (e g defects bet

A portable hemianopsia tester

By

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A portable hemianopsia tester (PHT) has been constructed It is a simple static perimeter consisting of a plate 15 x 20 cm in size with a central fixation light and four fixed test lights (light emitting diodes) one for each quadrant When the perimeter is placed 30 cm from the eye being examined the eccentricity of the test lights is 15 degrees Their intensity can be changed along a scale of ten steps with a ratio of $\sqrt{2}$ between adjacent steps One or two test lights or all four can be exposed simultaneously for 0 2 seconds Because of this short exposure time unsteady fixation is counteracted

The intention was that the PHT should constitute a supplement to the *confrontation test* in bedridden patients It has been tested in 60 patients with and without hemianopsia Control methods were the kinetic Goldmann perimeter the *tangent screen* and the confrontation test The PHT revealed all the total hemianopsias and quadrantanopsias and the majority of the relative defects Furthermore the PHT was also capable of disclosing hemianopsia in certain subjects who did not cooperate in conventional field examination including the confrontation test

To be published in full extent in Acta Ophthal (Kbh)

Visual field widening in retinitis pigmentosa

By

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Various magnifying devices have long been available to those with impaired central visual acuity Little however seems to have been done to assist those with severely restricted visual fields like retinitis pigmentosa or advanced glaucoma patients These may have good foveal vision but fields of ~-10° severely disabling them

There is a simple optical method for widening a concentrically restricted visual field In principle it is founded on the reversed telescope e g the Galilean (Holm 1970) Fundamental to the method is the idea of utilizing a highresolving area the fovea to receive information from a field much larger than normal While such field compressing means a smaller scale image on the retina this can be afforded if the original central acuity is reasonably intact In summa one trades acuity for field!

In practice visual field wideners can be constructed in several ways The most elegant may be to place a strong positive contact lens directly on the cornea and a strong negative lens in a regular glass-frame Experience demonstrates however that a more acceptable solution is a self-contained widening unit placed on a hinge on the patients eye-glasses Thus the patient is able to use either his normal' restricted field or for moving around and orientation purposes the expanded field seen through the widener

Two retinitis pigmentosa patients with fields of less than 10^{0} but central acuity of close to 20/20 have tried a 3 5x field increasing device for some time (Fig 1 2) Both express satisfaction but also describe problems 'It was possible to obtain a total perspective of something without scanning it was easier to spot obstacles in pathways so it was possible to avoid bumping into them but 'it was difficult to adjust to fast moving objects and it was difficult to move around in unfamiliar surroundings

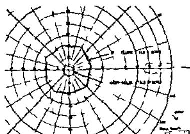


Fig 1

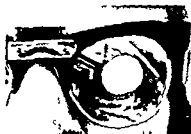


Fig 2

Further studies will show weather binocularity is feasible what degree of field increase is optimal etc The presently used device is being manufactured by Preisler Optical Co in Malmo Sweden

References

Holm O (1970) A simple method for widening restricted visual fields Arch Ophthal 84

Photography of the nerve fiber layer in retinal disturbances

By

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Fluorescein angiography in general anaesthesia - technique and indications

By

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Rapid sequence fluorescein angiography requires good cooperation of the patient Infants and small children as well as retarded patients and patients with nystagmus require general anaesthesia for photography

At the Helsinki University Eye Hospital a series of 47 patients aged 6 weeks - 25 years were examined by fluorescein angiography in general anaesthesia between May 1 1973 and May 1 1975 Six children were less than 6 months of age and eight over 10 years Nine children were examined twice for follow-up of progression and/or photocoagulation treatment 47 simultaneous electroretinograms were recorded

Most patients examined were sent for neuro-ophthalmological examination from the department of pediatric neurology The indications for fluorescein angiography were progressive encephalopathy suspicion of papilloedema optic disc anomalies and macular dystrophies Ophthalmologic indications were exudative and inflammatory retinal and choroidal diseases neoplasms and congenital malformations

Anaesthesia As premedication for anaesthesia atropine and almost regularly pethidine were administered Twelve children aged 9 months - 3 years were given enallynymal sodium rectally for induction of anaesthesia Five children preferred tiomebumal sodium induction intravenously to inhalation The anaesthesia method of choice (31 children) was 1-3 per cent halothane and 4 1 nitrous oxide/2 1 oxygen by mask This method excludes intubation - extubation complications Respiratory arrest occurred once and was immediately treated by controlled respiration and intubation Eighteen children of the early series got tiomebumal sodium and suxamethonium and were intubated Six children were given ketamine without intubation This method however was found unsatisfactory because of nystagmus and muscle twitching due to ketamine

Fluorescein photography After maximal dilatation with 0 5 per cent cyclopentolate twice and 2 5 per cent phenylephrine fluorescein angiography was performed using the Zeiss fundus camera with a Robot motor camera attached permitting 0 8 second intervals No suspencion device was used The head rest for the sitting patient was removed photography was performed with the anaesthesized patient lying on his side (Fig 1) An eye speculum was used to keep the lids apart and the eye was fixed in disired position by a muscle hook or forceps The same method was used for anterior segment angiography with the slitlamp



Fig 1

10 mg/kg body weight of fluorescein sodium (Fluorescite®) was injected in the preplaced canule Our filtercombination is a Baird Atomic 4 interference filter for excitation and a Kodak Wratten 15 absorptionfilter for absorption Kodak Tri X Pan film was used The films are developed in our own laboratory in Kodak D 76 solution 1 1 for 20 minutes in plus 20 degrees C Fixation Scanfors

For good quality pictures the method described has been of great value Expensive additional equipment is not needed for fluorescein angiography in children and other patients requiring general anaesthesia In assessing the indication for the procedure the risk of general anaesthesia must be taken into account

The effect of chloroquine on the retina and the nervous system

By

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The action of chloroquine on the metabolism of retinal ganglion cells and peripheral neurons was studied in acute and chronic experiments in rabbits Following an intraocular injection of 500 µg chloroquine into the vitreous body (equivalent to a concentration of 1 mM) the RNA synthesis and protein synthesis in the retina of albino or pigmented rabbits were not significantly changed in acute experiments (Karlsson et al 1975) Rabbit retina in vitro showed a marked inhibition of DNA RNA and protein synthesis when incubated in the presence of millimolar concentrations of chloroquine (Giuffrida et al 1975) Nodose ganglion/vagus preparations incubated in vitro in two-compartment chambers (McLean et al 1975) demonstrated that axonal transport was blocked by chloroquine when the nerve trunk was exposed to a concentration of 10^{-3}M of the drug

A parallel study in which albino rabbits were fed chloroquine (100 mg/kg body weight) 3 days per week for a period of six months showed no significant blockage of axonal transport in the vagus nerves Experiments on the axonal transport in the retinal ganglion cells of these rabbits are under way

The findings will be discussed in relation to the retinotoxic action of the drug

References

Giuffrida A M Sjostrand J Cambria A Serra I Vanella A Avitabile M Jarlstedt J and Karlsson J -O (1975) In vitro action of chloroquine on nucleic acids and protein biosynthesis in the rabbit retina Italseber Symposium Catania In press

Karlsson J -O Stella-Giuffrida A M Jarlstedt J Serra I and Sjostrand J (1975) Action of chloroquine on in vivo RNA and protein biosynthesis in the retina and the optic pathway of the rabbit Italseber Symposium Catania In press

McLean W G Frizell M and Sjostrand J (1975) Axonal transport of labelled proteins in sensory fibers of rabbit vagus nerve in vitro J Neurochem in press

Interplexiform cells A recently discovered retinal main cell type

By

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Fluorescence microscopy has revealed a new type of aminecontaining retinal neuron the interplexiform cell that extends processes in both plexiform layers After intravitreal injection of 5 6 dihydroxytryptamine in goldfish and Cebus monkey the processes of these cells can be identified by electron microscopy In goldfish the processes are pre- and postsynaptic to amacrine cells in the inner plexiform layer and presynaptic to bipolar and horizontal cells in the outer plexiform layer Interplexiform cells thus provide an intraretinal centrifugal pathway from inner to outer plexiform layers

The work was done in collaboration with Dr John Dowling Harvard

Light evoked release of glycine from rabbit retina

By

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Glycine is one of the amino acids now regarded as a putative neurotransmitter in the CNS In retina it is present in high concentration and an active high affinity uptake system into a type of amacrine cells has been demonstrated Glycine has an inhibitory effect in retina that is antagonized by strychnine Electrical stimulation and ionic shock are methods used to demonstrate the release of neurotransmitter in CNS but with such crude methods of stimulation glycine and other amino acids can be released also from tissues where they are unlikely to be neurotransmitters Demonstration of a release of glycine with a more physiological presynaptic stimulation would strongly support glycine being a neurotransmitter We have therefore studied the possibilities of releasing glycine from retina by light stimulation

Tritiated glycine was injected intravitreally in rabbits In good agreement with previous results the site of uptake of radioactivity into the retina was almost exclusively into a type of amacrine cells The eye was enucleated and the anterior segment and the vitreous were carefully removed The eye cup was placed in a small organ bath and superfused in darkness with a balanced salt solution After 20-30

minutes the retina was stimulated by light flashes The radioactivity of the superfusate was monitored by liquid scintillation spectrometry Light flashes increased the release of radioactivity significantly The start of the light flashes was varied and the increase in the release correlated exactly with it

Thin layer chromatograms of the superfusate demonstrated a single radioactive spot which co-chromatographed with authentic glycine The radioactivity of the glycine spots formed a peak matching that of the superfusate fractions

There was no appreciable change in the efflux of the radioactivity if the stimulation of light flashes was exchanged for continuous light The amacrine neurons are known to respond readily only to changes in illumination and thus the radioactivity seems to come mainly from the amacrine cells

If the temperature was changed from 37°C to +2 to +4°C there was no effect of light flashes The result demonstrates that the light induced release is dependent upon neural and/or metabolic activity and is not caused by a direct photochemical effect When tritiated valine is injected intravitreally it is taken up diffusely by the retinal cells In retinas loaded with ^{3}H-valine it was not possible to detect any light induced change in the efflux of radioactivity This might have been expected if the light induced release of radioactivity was the result of an unspecific reaction

The present demonstration that light stimulation will release glycine from the retina is one of the main criteria required in the proof that it is a neurotransmitter It is of particular importance that the release is caused by the stimulus that the tissue is normally intended to respond to

Importance of corneal thickness in applanation tonometry

By

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In several groups of non-glaucomatous patients a positive statistical correlation was found between central corneal thickness and intraocular pressure measured by applanation tonometry Normal corneal thickness was found in glaucoma simplex a thick cornea was found in ocular hypertension and a thin cornea in low-tension glaucoma

On the assumption that the thickness influences the measured value of the intraocular pressure as emphasized in the original papers of Goldmann readings with the applanation tonometer were made at various intraocular hydrostatic pressures and compared with central corneal thickness In human eyes with a normal corneal thickness tonometer readings and hydrostatic pressure coincide with thick corneas the readings were too high with thin corneas too low The correlation between corneal thickness and the error of applanation tonometry (ΔP) was statistically highly significant ($p < 0\ 001$) A table has been calculated showing the correction to be added to the applanation reading at the various corneal thickness-values The central corneal thickness is a parameter which should be taken into consideration when evaluating applanation tonometer readings

The AO - non contact tonometer

By

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The measurement of the intraocular pressure by a non contact tonometer was correlated to Goldmann tonometer in 20 normal persons 20 glaucomatous patients and 8 patients suffering from corneal diseases

The error in measurement for the non contact tonometer was related in normal persons to their skill of fixation and in the eye patients to height of pressure and to corneal state

Acceptable correlation was found between non contact tonometry and Goldmann applanation tonometry when the cornea was normal and the pressure below 35 mm Hg (Goldmann) otherwise the non contact tonometry was only guiding and in the presence of corneal disease unreliable

Good fixation reduced the methodical error The standard deviation was s 1 09 mm Hg at poor fixation and s = 0 60 mm Hg at good fixation

Repeated measurements on the same eye with non contact tonometry does not alter the intraocular tension

To be published in Acta Ophthal (Kbh)

Gonioscopic findings of importance for classification of glaucoma

By

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Gonioscopy is no new examination but with an improved and consistent technique new observations can be made and thus the method can be renewed

The gonioarchitecture is determining for the aqueous outflow and therefore gonioscopy plays a dominating role by classification of glaucoma According to Duke-Elder s System of Ophthalmology simple glaucoma must be a diagnosis by exclusion after that relevant angle anomalies and pre-existing ocular pathology have been excluded by gonioscopy In order to reach a meaningful discussion regarding the gonioscopic findings the introduction of a standardized microscopic technique is necessary as well as a generally accepted terminology based on the microarchitecture of the angle Today when both the examination technique and the terminology are poorly defined it is no surprise that the interpretation of the gonioscopic observations is a matter of dispute A gonioscopy lege artis requires a bright source of illumination a slit-lamp a microscope with a magnification of at least 16-32 X and a contact lens Without an examination in high magnification (32-40 X) with a very narrow slit the gonioscopy is incomplete

The following three classes of glaucoma will be illustrated by goniophotos drawings and scanning electron microscopic photos 1 Congenital glaucoma 2 pigmentary glaucoma and 3 exfoliation glaucoma

1 The basic maldevelopment in congenital glaucoma goniodysgenesis is usually easily demonstrated It must be remembered that this glaucoma can affect not only infants but also young and adult persons The typical goniofinding is a wide open angle crowded with an uveal meshwork and an endothelial covering In striking contrast to the excessive stroma in the angle the iris stroma is hypoplastic and thin often making the pigmentary layer of the iris visible

The angle stroma is seen to be covered by an endothelial membrane which at the line of Schwalbe is continuous with the corneal endothelium These gonioscopic observations are verified by scanning electron microscopic preparations

2 In pigmentary glaucoma the characteristic goniofinding is a thick band of secondary pigmentation In addition there is an excess of uveal meshwork crowding the wide open angle Therefore the angle in pigmentary glaucoma demonstrates the same basic maldevelopment as congenital glaucoma and can be regarded as a special variety of the latter

3 Exfoliation glaucoma is a well known entity in Sweden and constitutes approximately 50 % of all open angle glaucomas Two factors at least appear necessary for the development of exfoliation glaucoma an unknown often hereditary glaucoma factor and the exfoliation syndrome According to gonioscopic findings the unknown factor is equivalent to goniodysgenesis with the characteristic picture described above only not so conspicuous The combination of late congenital glaucoma in one eye and exfoliation glaucoma in the other eye of the same individual support this etiology of exfoliation glaucoma Further support is given by scanning microphotos

Summary According to gonioscopy and scanning electron microphotography maldevelopment of the angle or goniodysgenesis is a basic lesion in congenital glaucoma pigmentary glaucoma and exfoliation glaucoma Therefore approximately 85 % of all open angle glaucomas differ from simple glaucoma by displaying goniodysgenesis

Discussion (B Svedbergh Uppsala) Scanning electron microscopy on the pretrabecular membrane The existence and certain properties of the pretrabecular membrane was demonstrated by scanning electron microscopy in cases of late congenital glaucoma and exfoliative glaucoma

Factor VIII in aqueous outflow pathways

By

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Factor VIII (Antihaemophilic Factor A-von Willebrand Factor) is a protein involved in the first phase of blood coagulation and in the mechanism of platelet adhesion The localisation of this protein has been studied in the anterior segment of the human eye by a direct immunofluorescent method Factor VIII was found in the walls of aqueous outflow pathways but not in those of Schlemm s canal Having the endothelium of Schlemm s canal fibrinolytic activity this structure can be expected to be especially well protected against fibrin deposition and occlusion by platelets and thrombi The ciliary processes of the adult eye had no Factor VIII activity Instead FITC-fluorescence could be seen in the vessel wall of the ciliary processes of the foetal eye This difference may be connected with the function of aqueous secretion

<u>Amyl nitrite test in glaucoma simplex</u>

By

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The peripheral vasodilatory effect of amyl nitrite on the intraocular tension was examined in 31 patients with glaucoma simplex and 23 patients with cataract as the only ocular disease

Amyl nitrite was given as vitrellae for inhalation and the intraocular tension was measured with the Goldmann applanation tonometer before inhalation of amyl nitrite and 10 and 20 minutes following inhalation 25 of 31 patients with glaucoma simplex showed an average fall of intraocular tension per eye of 5.2 mm Hg applanation The average age of these 25 patients was 72.7 years The last 6 patients with glaucoma simplex showed no fall of intraocular tension after amyl nitrite The average age of this group was 52 years (40–57) a much younger group

The patients with cataract were examined in the same manner as the patients with glaucoma simplex The average fall of tension was 0.15 mm Hg applanation as opposed to the fall in tension of 5.2 mm Hg applanation in the older group of glaucoma simplex patients

The average age of the patients with cataract was 70.1 years and this group can therefore be compared with the similarly aged glaucoma simplex group whose tension fell following amyl nitrite

Inhalation of amyl nitrite results in a fall in the systolic blood pressure of [illegible]0 mm Hg

After 10 minutes the blood pressure returned to the original value

In connection with the fall in blood pressure the pulse increases This is due to a vagus reflex via glomus caroticus

Whether it is this reaction on the parasympathetic system which causes the intraocular fall of tension is at present under investigation

In conclusion it can be said that the effect of amyl nitrite on the *intraocular pressure* in elderly patients with chronic glaucoma can *be safely used* as a test Compared with other provocative tests the tension in the eye is lowered by amyl nitrite

Acetazolamide used diagnostically on suspicion of disease in the circulation of the aqueous humour Comparison with weight tonography (preliminary results)

By

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Pressure decays after intravenous acetazolamide have been recorded simultaneously from the two eyes in about 80 patients in a sitting position by alternating applanation tonometry (as described by Nissen and Hoppe 1974) In the control period (10-20 minutes) the two pressures adjust themselves at levels which are often a few millimeters lower than the first readings At time zero 10 mg of acetazolamide per kg body weight is injected intravenously the alternating pressure measurements are resumed and the pressure decays recorded - In these test curves attention was payed to the following parameters a) the first pressure readings b) the stable pressure levels late in the control period c) the stable pressure levels reached after the acetazolamide d) the outflow facilities estimated by comparison with reference curves (see below) e) breaks in the test curves f) the degree of similarity between the curves of the two eyes - The reference curves were calculated on the following assumptions

1) A fast reduction in the rate of formation of chamber fluid to a constant level (a step fall) due to the acetazolamide

2) Friedenwald s pressure-volume relation of the eye with a scleral rigidity of 0 0215

3) Poiseuille s law of the drainage routes for chamber fluid leaving the eye with varying values of the constant of proportionality of the formula (the outflow facility C)

4) Constancy of the episcleral vein pressure

The appearance of the test curves made it possible to separate the following group of eyes with intraocular hypertension and open angles from the rest The estimated outflow facilities were above 0 15 (0 12) µl min^{-1} mm Hg^{-1} and the pressure curves of the two eyes in a pair were very similar and matched the hypothetical reference curves well None of these eyes had visual field defects In the remaining open-angled hypertensive eyes the curves were unidentical and half of them showed irregularities (breaks) Outflow facilities estimated from approximately matching reference curves were below 0 15 Two thirds of these pairs had defects in the visual fields The curves from 4 out of 7 eyes with narrow angle glaucoma showed pronounced breaks one of them to such a degree that the curve was biphasic - In simple glaucoma the outflow facilities estimated by weight tonography agreed fairly well with those judged from the acetazolamide curves both were below approximately 0 15 In the special group of symmetric intraocular hypertensive eyes without function loss the tonographic values were mostly appreciably lower than the acetazolamide values the latter were in general between 0 15 and 0 4

References

Nissen O I and Hoppe R (1974) The facility of aqueous outflow calculated from the rate of fall in applanation pressure after intravenous acetazolamide in man Acta Ophthal (Kbh) 52 390–405

Clonidin effect on the intraocular pressure and eye circulation

By

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Applanation tonometry tonography blood pressure measurement and fluorescein angiography of the fundus and limbal area were done to 19 patients Seven had simple three capsular and four low tension glaucoma Five patients had glaucoma suspicion 0 125 % and 0 25 % clonidin in methylcellulose solution was dropped three times a day in both eyes

IOP was lowered from 20 to 29 per cent outflow facility improved from 5 to 15 per cent Po/C ratio was from 17 to 31 % smaller Blood pressure dropped 8-12 % in systole and 7-16 % in diastole There was no practical difference between the 0 125 % and 0 25 % solution in the IOP lowering but the side effects as lowered blood pressure dry mouth sleepiness and dizziness were more disturbing when the stronger drug was used

The limbal circulation became 17 % slower than without the drug In the fundus the arterial phase was slowered 32 % and the venous phase 41 % The arterial diameter changed minimally becoming 0 5 % thicker The veins became 8 per cent thinner

Follow up Seven patients from 14 had fair primary response to the drug Four of them were low tension patients Three of them felt a great discomfort and could not use the medicin The fourth has good pressure but the field defect is growing One simple glaucoma patient has had six months good pressure and no symptoms One has fair pressure but the visual fields are getting worse The third has poor pressure and he uses usula drugs too In the capsular glaucoma group the primary result was poor

Clonidin has a great effect on the circulation One could not show a direct undesirable effect on the nerve head circulation But it seems that the former speculations of the real benefit of the clonidin in the glaucoma therapy should be kept in mind Perhaps new methods as cine angiography or visual field examination with artificially elevated eye pressure will give the answer

Direct fluorometric measurement of aqueous humour flow

By

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The technique which can be used for a direct measurement of aqueous humour flow in an intact eye has been developed

Sodium fluorescein (25 mg/kg) is injected intravenously and blood samples are taken with certain intervals for fluorometric analyses of the blood sodium fluorescein concentration during the experiment Blood samples are centrifuged serum proteins are precipitated by perchlorid acid at 37° and sodium fluorescein concentration is measured with a fluorometer

Simultaneously is the sodium fluorescein concentration evaluated in the studied eye with a special measuring device developed for this purpose This device contains a fluorometer from which the exciting light (470 nm) is conducted via a glass fiber to the eye The tip of the glass fiber is one millimeter in front of the cornea Another glass fiber is in an angle of 60 degrees to the exciting fiber and conducts the emitting light (520 nm) back to the fluorometer This is conducted to a pen recorder

With a mathematical model constructed in accordance to Goldmann (1950) the flow of sodium fluorescein into the eye is calculated These calculations are based on two linear mathematical equations which are solved by a programmed computer

With the technique described we have found that in the normal rabbit eye the flow is 2 66 ± 0 77 µl/min

Aspects of the influence of parasympathetic stimulation on aqueous humour dynamics in the rabbit

By

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Parasympathetic stimulation has been performed by stimulating the oculomotor nerve intracranially with a stereotactic technique Electron microscopical biochemical manometrical and fluorometrical methods have been used to measure the changes in the blood-aqueous barrier as well as in aqueous humour dynamics and contents The conclusions made here are based on the results of about 80 experiments performed on rabbits

It has been shown that during parasympathetic stimulation clear-cut morphological changes occur in the blood-aqueous barrier Vesicles of different size appear in both the layers of the ciliary epithelium (Uusitalo Stjernschantz and Palkama 1974) The protein content of the aqueous humour is also altered after parasympathetic stimulation being two- or threefoldly increased as compared with that of the normal eye (Stjernschantz Palkama Uusitalo and Renkonen 1973)

Manometrical studies using the technique described by Sears and Bárány (1960) show that the most constant feature of parasympathetic stimulation is an increase in the outflow facility of aqueous humour This tends slightly to decrease IOP Inflow of aqueous humour was also increased but in this respect the results were somewhat inconsistent (Stjernschantz 1975)

Fluorometrical studies show that after intravenous injection sodium fluorescein is concentrated in a considerably greater amount in the stimulated eye as compared with the normal eye Using a computer analysis of a mathematical model this was interpreted to be due to a moderately increased inflow of aqueous humour (Stjernschantz Koivo and Palkama 1975) The results are however not final and studies are going on to evaluate the importance of the increased permeability of the blood-aqueous barrier in this respect

As a conclusion it may be summarized that a parasympathetic stimulation seems firstly to alter the permeability of the blood-aqueous barrier secondly to decrease the IOP by increasing the outflow facility of aqueous humour and thirdly slightly to increase the inflow of aqueous humour which however has to be further investigated

References

Sears M L and Bárány E H (1960) Outflow resistance and adrenergic mechanisms Arch Ophthal 64 839-848

Stjernschantz J Palkama A Uusitalo R and Renkonen O -V (1973) Aspects of the blood-aqueous barrier with special reference to the penetration of antibiotics Acta Ophthal (Kbh) Suppl 123 69-74

Stjernschantz J (1975) Effect of parasympathetic stimulation on the intraocular pressure inflow and outflow facility of aqueous humour in curarized rabbits In prep

Stjernschantz J Koivo A and Palkama A (1975) Studies on the inflow of aqueous humour in the intact rabbit eye during parasympathetic stimulation In prep

Uusitalo R Stjernschantz J and Palkama A (1974) Studies on parasympathetic control of the blood-aqueous barrier in the rabbit An electron microscopic study Exp Eye Res 19 125-134

Episcleral venous pressure and pregnancy

By

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The episcleral venous pressure (P_v) can be measured by directing a stream of air against a vessel and noting at which air pressure a collapse is provoked (Krakau et al 1973)

It is known that repeated applanation tonometry once a minute during five minutes provokes an IOP reduction by about 3 mm Hg (Moses 1961 Bechrakis 1966 Wilke 1972) Loading of the eye by a small weight or by repeated applanation tonometry elicits changes in the episcleral recipient venous pressure (P_{rv}) (Krakau and Wilke 1974)

In pregnancy there is a change in general blood circulation with lower peripheral resistance in the vessels and increased minute volume It has also been shown that the IOP and the amplitude of the puls-synchronous IOP variations are reduced in pregnancy (Hørven and Gjønnaess 1972)

In a series of 20 pregnant women in the last trimester and another group of 20 nonpregnant women the effect of repeated applanation tonometry was investigated In the latter group there was as could be expected a significant IOP reduction by about 3 mm Hg but in the pregnant group no reduction could be established (Fig 1) The IOP in the group of pregnant women was 1 4 mm Hg lower than that of the normal group which confirms earlier observations

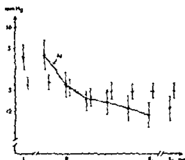


Fig 1

Repeated applanation tonometry in 20 normal (N) and 20 pregnant (P) women

Six women with outstanding recipient episcleral veins were investigated during and after and in two cases also before pregnancy The P_{rv} was recorded before during and after loading of the eye with a weight of 2 5 gr for 3 minutes Before and after pregnancy a significant pressure reduction was observed in the P_{rv} at loading of the eye In pregnancy the P_{rv} was reduced and there was no effect during loading of the eye (Fig 2)

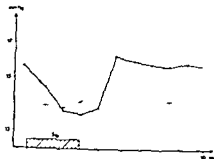


Fig 2
Episcleral venous pressure (+++) during loading of the eye with 2 5 gr in three minutes in six women during (P) and after (A) pregnancy

The present finding reflects the general effect of pregnancy on the peripheral circulation It seems likely that the venous pressure reduction causes the IOP reduction in pregnancy and we have thus given evidence of an extraocular mechanism which under physiological conditions influences the IOP

References

Bechrakis E (1966) Uber den spontanen Druckabfall bei Applanationstonometrie Ophthalmologica 151 604-614

Hørven I and Gjönnaess H (1972) Corneal indentation pulse reduction in pregnancy Acta Ophthal (Kbh) 50 375-384

Krakau C E T Widakowich J and Wilke K (1973) Measurements of the episcleral venous pressure by means of an air jet Acta Ophthal (Kbh) 51 185-196

Krakau C E T and Wilke K (1974) Effects of loading of the eye on the intraocular pressure and on the episcleral venous pressure Acta Ophthal (Kbh) 52 107-124

Moses R A (1961) Repeated applanation tonometry Ophthalmologica 142 663-668

Wilke K (1972) Effects of repeated tonometry genuine and sham measurements Acta Ophthal (Kbh) 50 574-582

Wetting time

By

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The wettability of the cornea (wetting time = B U T - break up time) is measured in the following way

The patient is placed at the slit lamp in half-lit room One drop of fluorescein 0 125 % is instilled in the conjunctival sac (or Kimura fluorescein paper is used) The patient is requested to blink a few times A stop watch is started immediately after the last blink Using an about 1 mm broad oblique cobalt-filtered light beam the whole fluorescein-stained precorneal film is searched from side to side for beginning holes in the film The button of the stop watch is pressed at the first sign of a hole

The patient has to keep his eyes open during the examination by aid of his will alone the eye lid must not be supported

The normal value is ≧10 sec with no age or sex dependence (Norn 1969 Lemp et al 1973)

Increased wetting time means better wettability increased surface activity decreased surface tension diminished contact angle

The wettability depends mostly upon the surface active agents (fat acids stearin acids etc) between the superficial oily layer and the aqueous fase of the precorneal film (Berger 1973)

The wetting time is reduced in relation to reduced secretion of tears (keratoconjunctivitis sicca) reduced mucus (pemphigoid) or destruction of the deep layer of the precorneal film (keratitis erosio corneal oedema graft lagophthalmos)

In all these cases the wetting time can be increased by means of mucomimetica (methylcellulose polyvinylalcohol B P -polymer)

Mucomimetica are indicated in the dry eye syndrome (that means conjunctival complaints with wetting time < 10 sec) They are further used as contact lens wetting solutions and as vehicles prolonging the contact time of the pharmacon

On the other hand ointment and oil deminish the wetting time Simple ointment (oculent simplex D A K 80 % vaselinum and 20 % liquid paraffinum NFN) reduce 7 02 ± 1 04 times simple ointment with 20 % silicone oil reduce 3 72 ± 0 63 times and simple ointment emulsion (oculent simplex Ph D 48 with adeps lanae and alcohol cetyl) reduce the wetting time 1 79 ± 0 21 times (±SEM) In many cases they nevertheless increase the contact time

It is surprising to find that ointment works in an opposite way from the methyl-cellulose concerning wetting time and yet both prolonge the contact time (Norn 1975)

Mucomimetica protect cornea ointments break the precorneal film with some destruction of the corneal epithelium

References

Berger Robert E (1973) Precorneal tear film mechanics and the contact lens (Diss) p 241 Dept of Mechanics and Materials Science The John Hopkins University of Baltimore In manuscript Baltimore

Lemp Michael A and Hamill John R (1973) Factors affecting tear film break up in normal eyes Arch Ophthal 89 103-105

Norn M S (1969) Desiccation of the precorneal film Acta Ophthal (Kbh) 47 865 880

Norn M S (1974) External eye (methods of examination) p 199 Scriptor Copenhagen

Norn M S (1975) Correspondance (topical fluorescein penetration) Am J Ophthal 79 335

Determination of tear flow using a radioactive tracer

By

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The rate of human tear secretion under basal circumstances is an elusive quantity to measure A value less than one gram per day is usually reckoned Most methods implicate some irritation to the eye causing rapid fluctuations in the normal tear flow Methods causing no stimulation to the eye at the time of determination are to be preferred

Using a radioactive tracer and an appropiate detection system tear flow can be determined without touching the eye after instillation The detection system consists of a gamma camera with a pinhole collimator coupled to a digital system Recording and storage of information are controlled by a minicomputer and data are delivered for long-term storage on a magnetic tape

The tracer used was Tc 99m which is available in nuclear medicine departments as sodium pertechnetate Tc 99m has a half-life of 6 hours and is primarily a gamma emittor The dose to the lens is small and repeated determinations can be performed

The subject is placed in a supine position with his head fixed The technetium was contained in 10 µl of a normal saline solution which was placed on the cornea The distribution of Tc in the conjunctival sac canaliculi lacrimal sac and nasolacrimal duct could be followed on an oscilloscope Scintophotos were made at the beginning and at the end of the determination

By the region of interest technique the elimination of Tc from the conjunctival sac was followed in 15 minutes The data system produced an activity-time function curve representing the fall-off of radioactive material in the designated conjunctival sac area The decay of activity could be interpreted as an exponential elimination A semilog plot of activity versus time showed that the elimination was initially fast in the first 5 to 7 minutes in most cases followed by a slower physiologic decay The data system approximated an exponential curve to the actual curve and calculated the rate of elimination (k-value) from this approximated curve

The distribution of the k-value from 50 determinations on normal eyes was shown the average being 0 079 min^{-1} ± 0 040 (2 x standard deviation) for the basal elimination The elimination rate was 2 to 3 times greater in the initial fase

Other writers have found that the tear volume in the conjunctival sac increases only very slightly with increasing tear flow Assuming a tear volume of 7 µl the tear secretion in the basal fase was calculated to be 0 6 µl min^{-1}

The determination of tear secretion by this method is performed with minimal stimulation to the eye Tear flow in the conjunctival sac in toto is measured The equipment is commonly available in nuclear medicine departments The method is a useful tool to study the anatomy and pathology of lacrimal drainage and the dynamics of tear flow in various pathologic and pharmacologic conditiones Some of these aspects will be the subject of a future publication

Prophylaxis of allograft reaction in corneal grafting

By

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Purpose of our survey is to study the occurrence of corneal graft reaction or graft rejection and its prevention by using HL-A compatible donor cornea and immunosuppressive therapy The material totalled 86 successive corneal graftings 6 of them were excluded for various reasons Observation period varied from 6 years to 3 months Except HL-A tissue typing even ABO determination and cross-matching test were performed 1969-72 only fresh corneas from the moist chamber (+4°C) were available It lead to few and fairly poor matches as to untyped donor material 1973-75 during the cryopreservation period 27 good matches (0-1 mismatches) were gained (Group I) They were compared to 19 graftings with 2-4 mismatches between the donor and the recipient (Group II) and 34 graftings with untyped donor cornea (Group III)

In vascularised corneal beds allograft reaction developed in 24 % and in non-vascularised cases in 11 % The frequency of allograft rejection in group I (0-1 mismatches between donor and recipient and 54 % of recipient corneas being vascularised) was 4 % when it in group II with 2-4 mismatches was 21 % and in the untyped group 22 %

Survey will continue However it seems in this phase that well-matched donor cornea failing none or one HL-A antigen prevents allograft reaction even in vascularized corneal bed one exception out of 27 pairs might point to that even HL-A compatible foreign cornea is not fully safe possibly due to the effect of LD antigens or the antigens of other loci

Irreversible mydriasis following keratoplasty in keratoconus

By

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Most papers dealing with keratoplasty in keratoconus do not mention the complication of postoperative irreversible mydriasis which seems to be specific for this disease It is not the mydriasis itself but the danger of secondary glaucoma which constitutes the main clinical problem of this complication Spontaneous postoperative dilatation of the pupil has seldom been observed in eyes which have been grafted for other corneal diseases even if using identical surgical technique One therefore has to conclude that patients with keratoconus in addition to their corneal dysplasia must have some defect which makes them prone to this specific complication when subjected to intraocular surgery

In our material 62 eyes were grafted for keratoconus 11 eyes developed mydriasis In five of the affected eyes mydriatics were used postoperatively In these patients the mydriasis was discovered 2 3 weeks postoperatively Six of the affected eyes had no mydriatics postoperatively In these patients the mydriasis was discovered 1-4 days postoperatively The use of mydriatics postoperatively does not seem to play any part as an aetiological factor

A neuro-chemical defect of the innervation of the sphincter or the dilator muscle has been considered as a possible cause A preoperative test of the pupillary reactions on eyes with keratoconus have not however revealed any difference from normal eyes Mydriatics or miotics acting on the muscles do not provoke or prevent a postoperative irreversible dilatation of the pupil The power of accommodation was found to be normal in these patients

The mesoderm surrounding the rim of the optic cup gives rise both to the stromal layer of the iris and the stroma of the cornea We have therefore made a thorough clinical examination of the iris in the unoperated eye with the slit lamp and

diascleral transillumination Examination with fluorescein angiography of the iris is in progress 35 patients were examined In these examinations we have found that patients with keratoconus very frequently shows an apparent hypoplasia of the iris stroma In most cases a diffuse stromal rarefaction was seen the sculpturing of the iris was flattened and poorly marked especially in the area peripheral to the collarette In some patients there were some small defects in the stroma baring the underlying pigment epithelium

Irreversible mydriasis seems to be a fairly frequent complication In our opinion the mesodermal defect in keratoconus is not always confined to the cornea but very often also includes a hypoplasia of the iris stroma We postulate that this hypoplasia plays a decisive role in the development of the postoperative mydriasis The exact mechanism however is still not known

Simultaneous thermal recording of corneal temperature and blinking frequency in simulated arctic conditions

By

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To be published in Acta Ophthal (Kbh)

A semiquantitative enzyme assay for corneal collagenase

By

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The activity of crude corneal collagenase from the alkali-burned ulcerating rabbit cornea has been measured in a capillary tube assay system using unlabeled native reconstituted acid-soluble rat tail collagen as substrate By restricting the diffusion of enzyme to one dimension in the tube gel an high sensitivity has been achieved

The assay uses 50 µl capillary tubes length 67 mm containing 40 µl collagen gel in a concentration of approximately 1 mg/ml and 5 µl enzyme solution

In the assay system the initial rates of lysis are approximately proportional to enzyme concentration in the range of lytic values 0 03 mm/h - 0 4 mm/h Crude corneal collagenase has been measured at concentrations down to concen-

trations found in the growth medium from the 4-7 day of organ culture of rabbit corneas For comparison clostridiopeptidase A has been measured at concentrations down to 1 5 x 10^{-3} μg/ μl

The precision high sensitivity and simplicity of the assay system in addition to the minimal equipment required recommend its use in the screening for collagenase activity in biological fluids as f i in growth mediums from organ cultures of bank corneas

Autonomic and somatic sensory nerves of the iris and cornea

By

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Innervation of the albino rat iris and cornea was studied by using the formaldehyde-induced fluorescence technique the Lewis-Shute thiocholine method and $KMnO_4$ fixation Also the cat dog and rabbit eyes were used in some experiments In order to verify the routes of different nerve types to the anterior segment of the eye the following denervations were performed extirpation of the superior cervical and/or the ciliary ganglions and/or stereotactic coagulation of the ophthalmic nerve All possible combinations of the denervations were also done

All the adrenergic (fluorescent) fibres of the rat iris and cornea disappeared after ipsilateral superior cervical ganglionectomy Most of the iridic adrenergic fibres disappeared as well after ophthalmic neurotomy In the corneal stroma no adrenergic nerves were observed after this operation Ciliary ganglionectomy caused a slight decrease in the number of the adrenergic nerves in the iris but in the cornea no such effect was observed When ciliary ganglionectomy was combined with ophthalmic neurotomy all adrenergic fibres disappeared from the iris The rat cornea seemed to have less adrenergic nerves than the other species studied

Cervical sympathectomy had no effect on the AChE-containing nerves of the iris Ciliary ganglionectomy caused degeneration in most iridic AChE positive fibres After this operation it could be observed that the thin fibres in the sphincter area were degenerated whereas in the dilator area some of the thin fibres and the AChE positive nerve bundles remained intact All corneal AChE-positive nerves appeared intact after ciliary ganglionectomy Ophthalmic neurotomy caused disappearance of the thick nerve bundles from the dilator region of the iris other AChE-positive nerves were not affected The operation also destroyed all the fine fibres of the corneal epithelium The thick nerve bundles in the stroma of the cornea degenerated even though some AChE activity remained The iris and limbus but not the cornea contained myelinated nerve fibres which had AChE activity on their axolemma The axolemma of unmyelinated nerves in the iris and cornea was also stained

In the $KMnO_4$ fixed irides all myelinated fibres degenerated after ophthalmic neurotomy. Other denervations had no effect on these nerves.

It may be concluded that all the adrenergic fibres of the rat iris and cornea originate from the superior cervical ganglion and most of them run to the iris via the ophthalmic nerve. A minor part seems to contribute the sympathetic root of the ciliary ganglion and to enter the iris in the short ciliary nerves. The corneal adrenergic nerves are supposed to come exclusively with the long ciliary nerves.

Most of the AChE-containing nerves of the iris seem to originate from the ciliary ganglion which, however, does not transmit any AChE-positive fibres to the cornea. All corneal and part of the iridic AChE-positive nerves seem to be branches of the ophthalmic nerve and presumptively sensory. The myelinated nerves of the iris originate exclusively from the ophthalmic nerve.

Opacification at traumatic cataract

By

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Perforating lens injuries will generally cause a progressive cataract Even if the lesion is confined to the anterior lens cortex the opacification will be most apparent in the posterior subcapsular region No sufficient explanation has been given to this progressive posterior opacification

The structural and functional changes were studied in rat and rabbit lenses with experimentally induced traumatic cataract After injury to the anterior lens cortex the lenses were studied at different time intervals The lenses were examined histologically and by a quantitative microradiographic technique At certain stages lenses were also studied by electronmicroscopy and fluorescence microscopy utilizing different tracer substances

Posterior subcapsular opacities were observed 2 days after injury and a dense posterior cataract had generally developed after 3 weeks Histological and electron microscopical examinations of the posterior subcapsular region immediately after injury revealed more vacuoles in the damaged lens than in the non-damaged fellow lens The penetration of extracellular tracer substances was enhanced at the site of the injury

A decreased protein concentration corresponding to an increased water uptake was determined in the subcapsular cortex This change was somewhat more pronounced in the posterior cortex

These changes are most likely due to an increased uptake of sodium The reason for these changes is the damage to the lens epithelium The fiber cells have only a limited capacity of control of their ionic content and are thus dependent on a constant ionic milieu

The distinct interface between the relatively healthy inner cortex and the outer hydrated subcapsular cortex will act as a strong light scattering source This scattering of light will be much more intensive at the posterior cortex where light passes from a region with higher refractive index to the hydrated subcapsular region with a low refractive index

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Effects of X-ray irradiation on the ultrastructure of the lens epithelium and its sodium-potassium activated adenosine triphosphatase (Na-K-ATPase) activity

By

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The effects of ionizing radiation on adult rat lens were investigated by biochemical histochemical and electron microscopic methods

The left eye of each animal was exposed to an air dose of 1500 r of X-rays and the other parts were protected against the radiation by a lead sheet 5 mm thick The animals were kept under sodium pentobarbital anaesthesia during the irradiation

At intervals of 3 7 30 60 and 90 days after the irradiation the rats were killed and Na-K-ATPase activity of both the irradiated and control lens epithelium was studied biochemically and histochemically For electron microscopy samples were taken from different parts of the lens

At three days after the irradiation the first ultrastructural abnormalities were found in the epithelium and superficial cortex of the equatorial and posterior area The cytoplasm of some epithelial cells appeared vacuolated In the superficial cortex of the equatorial zone the intercellular spaces formed cystic dilatations In the posterior zone some cortical fibres were electron dense and showed some intracellular vacuoles

At seven days after the irradiation the epithelial cells became irregular in shape Some of the cells were large and oedematous whereas part of the cells showed an increase in electron density and appeared shrunken The epithelial intercellular spaces were enlarged with frequent lacunae The cytoplasmic material was rather coarse and irregular especially in the equatorial and posterior fibres Some posterior fibres were darkly stained and contained vacuoles The smaller vacuoles seemed to coalesce to form large vacuoles In cross sections the typical hexagonal shape of the lens fibres had disappeared and the fibres were almost round due to swelling

During the next 30 60 and 90 days after the irradiation the abnormalities appeared more advanced The relative amount of both shrunken and swollen epithelial cells of irregular shape and size was increased The cortical fibres showed irregular configuration and the gradient of the granularity in the cytoplasm was pronounced Large rounded vacuoles were observed especially in the equatorial zone The most prominent change at 90 days after the irradiation was the extreme increase of small vacuoles in the posterior cortex and almost total disorganization of the fibres in this area At this stage the first biomicroscopically visible signs of opacities of the lens were seen

No histochemically visible changes in the Na-K-ATPase activity were seen earlier than 30 days after the irradiation. In normal lens epithelium the reaction product is localized purely on the cell membranes. Thirty days after the irradiation the precipitation had diffused throughout the cytoplasm of the equatorial cells. However no biochemical change in the enzyme activity was noted.

The present results suggest that the lens epithelium is primarily damaged by X-ray irradiation. The Na-K-ATPase dependent ion pump system of the epithelium seems to be in some way affected as demonstrated histochemically. This change combined with the cell destruction could explain the osmotic disturbances in the lens. It is evident from these studies that marked ultrastructural changes of the lens were demonstrable long before any clinically visible alterations could be observed.

Evaluation of diagnostic tests based on uveitis survey at the Oulu University Eye Hospital

By

M. Saari and R. Miettinen

University Eye Hospital, Oulu, Finland

There are many reports on uveitis surveys in Scandinavia (e.g. Oksala 1960, Bergaust 1962, Leira 1965, Norn 1963) and elsewhere (Perkins 1961, Schlaegel 1965, Consul et al. 1972) but not in northern Finland. In order to establish the aetiology of uveitis in northern Finland, to modernize our uveitis survey to make it correspond to local circumstances, and to clarify the factors predisposing the patient to uveitis, we re-examined the 653 uveitis patients treated at the Oulu University Eye Hospital during the years 1964-1974 and evaluated the significance of the diagnostic test used. By means of active family history and determination of HL-A antigens we studied the genetic background of uveitis.

Of the 653 patients 321 were men and 332 women. 547 had anterior, 64 posterior and 42 generalized uveitis. 524 unilateral and 129 bilateral. 570 acute and 83 chronic, and 446 single and 207 recurrent. The aetiologic factors were distributed into rheumatoid (7.2 %), streptococcal (4.1 %), tuberculosis (3.7 %), toxoplasmosis (3.3 %), varicella-zoster (1.7 %), sarcoidosis (1.4 %), staphylococcal (1.1 %), leptospirosis (0.6 %), lymphatic leucaemia (0.5 %), herpes simplex (0.5 %), yersinosis (0.1 %) and undetermined cases (75.8 %). There were no cases of syphilis or histoplasmosis.

The determination of haemoglobin, red cell count and blood sugar were of little significance in surveying uveitis. The total white cell count was pathological in 53 and the differential in 20 cases of the total material. The ESR was increased in 188 and the urinalysis pathological in 1 cases of anterior uveitis. There were higher-than normal AST titres in 14 % of all cases. Latex, Waaler Rose and ASTA titres were significantly increased in many cases of iritis and toxoplasma serology

Movement of horseradish peroxidase in the anterior parts of the eye

By

A M Tønjum

Eye Department Rikshospitalet Oslo Norway

Evidence for vesicular transport across the endothelium of excised rabbit corneas has recently been published The present paper describes the distribution patterns of horseradish peroxidase in the anterior parts of dead rabbit eyes in situ and freshly enucleated vervet monkey and human eyes when the anterior chamber had been perfused by a cannula through the pars plana Attention was paid to those experiments where perfusion of the marker dissolved in Krebs-Ringer-bicarbonate solution with glucose was done for one hour Emphasis was put on the gross distribution pattern as studied in frozen sections incubated with hydrogen peroxide and diaminobenzidine During this incubation dark reaction products were processed in the tissues

In the rabbit eyes there was some staining of the stroma of the iris and the ciliary body However a much more intensive staining was present in the cornea particularly in the limbal region and the neighbouring sclera After the one hour of perfusion the posterior part of the central cornea was more intensively stained than the anterior part In the monkey and the human eyes there was only a faint staining of the ciliary body by the exogenous peroxidase whereas the staining of the corneas was similar to that of the rabbit corneas There was a sharp border between the cornea and sclera and the ciliary body These findings indicate that a transcorneal and a corneo-scleral movement of the tracer takes place and that this movement at least in the dead monkey and human eyes soon after enucleation appears to be more comprehensive than the uveo-scleral movement though the ciliary body and the sclera The transcorneal movement of horseradish peroxidase is to a major extent dependent upon an active vesicular transport across the endothelium and it is thus not necessarily indicative of a bulk flow of fluid along this route

The Descemet s membrane was intensively stained as compared to the stroma indicating that the Descemet s membrane is more porous or having relatively smaller excluded volumes than the stroma

Electron microscopic studies on the effects of prostaglandins on the blood-aqueous barrier of the rabbit eye

By

O Ø Pedersen

University Eye Hospital and Institute of Pathology Electron Microscopic Laboratory Rikshospitalet Oslo Norway

To be published in Acta Ophthal (Kbh)

The aqueous flare inducing effect of prostaglandin and α Melanocyte stimulating hormone

By

E Bengtsson

Department of Experimental Ophthalmology University of Lund

Lund Sweden

When applied topically to a rabbit eye prostaglandin (PG) gives an inflammatory reaction with a breakdown of the blood-aqueous barrier and an increased intraocular pressure (Waitzman and King 1967) This reaction is seemingly identical with that seen after different chemical and mechanical traumata to the eye and prostaglandin is suspected to be the common mediator of these traumatic agents (Beitch and Eakins 1969) Prostaglandin is supposed to exert its effect by increasing the intraocular level of cyclic adenosine 3 5 -monophosphate (cyclic-AMP) (Waitzman 1970) Agents that counteract this increase of cyclic-AMP either by inhibiting its formation or by stimulating its degradation should be able to antagonize the prostaglandin effect Imidazole has a stimulating effect in vitro on cyclic-AMP phosphodiesterase (Butcher and Sutherland 1962) which enzyme degrades cyclic-AMP to the metabolically inactive adenosine 5 monophosphate It has been reported that imidazole inhibits the increase in intraocular pressure induced by topical prostaglandin E (PGE) (Zink et al 1973 1975) and by topical arachidonic acid (AA) (Puig-Larellada et al 1975) which is the precursor of prostaglandin E Traumatic agents that exert their effect via prostaglandin should as well be inhibited by imidazole

The ability of imidazole to affect the inflammatory reaction to different traumatic agents was studied by photoelectrical measurements of the aqueous flare (AF) seen in the anterior chamber due to the protein leakage (Bengtsson et al 1975) The aqueous flare was measured in arbitrary units every half an hour until the maximum flare was covered The results are given as

Q_{max} values = $\frac{\text{maximum flare density after treatment}}{\text{flare density before treatment}}$

In the first experiment one eye of a rabbit was pretreated with 50 µl imidazole (100-200 mg ml^{-1}) locally applied to the cornea One to two hours later the following agents were administered

local application of 5 µg prostaglandin $E_2(PGE_2)$ to both eyes

2 drops of 2 % arachidonic acid (AA) to both eyes

infrared irradiation of the iris (IR) of both eyes

20 µg/kg α-melanocyte stimulating hormone (α-MSH) given subcutaneously

The results are given in Table I

In the second experiment pretreatment with imidazole was given by intraperitoneal injection of imidazole (250 mg/kg) Three hours later the same agents as in the first experiment were administered The results are given in Table II

Topical treatment with imidazole had no effect on the breakdown of the blood-aqueous barrier after stimulation with PG AA and infrared irradiation The AFR to α-MSH on the other hand was strongly potentiated and facilitated by topical imidazole in the eye These results support the suggestion that α-MSH exerts its effect on the blood-aqueous barrier in a way different from other traumata to the eye (Bengtsson et al 1975)

Intraperitoneal treatment with imidazole inhibited the breakdown of the blood-aqueous barrier elicited by PG AA infrared irradiation and α-MSH The reason why locally and systemically administered imidazole affects the α-MSH response in different ways is unclear The capacity of imidazole to affect water permeability calcium binding pH and osmolarity might contribute to its action on the α-MSH effect (Zink et al 1973 Puig-Parellada et al 1975) Pilocarpine (2 %) which has some chemical structures in common with imidazole was tested in a preliminary study (5 rabbits) for its possible effect on the AFR to α-MSH A facilitation nd potentiation of the AFR to α-MSH similar to that of locally administered imidazole was found

T ble I

Effect of topical imido ole on the aqueous flare response (in Q_{ma} alues)

Stimuli	Eyes pretreated with imidazole			Untreated eyes		
	mean value	range	no of eyes	mean value	range	no of eyes
PGE_2	21.0	10 46.0	8	18 1	6 55.0	8
AA	7 6	4 12.5	4	7 1	4 12 5	4
IR	9.7	1 16 0	7	10.8	6.3 24 0	7
MSH	12.8	4 32.0	9	6.0	1 0 30 0	9

Table I

Table II

Effect of intraperitoneal imidazole on the aqueous flare response (in Q_{max} values)

Stimuli	Eyes pretreated with imidazole			Untreated eyes		
	mean value	range	no of eyes	mean value	range	no of eyes
PGE_2	7.3	1.0 20.0	14	22.5	7 40	14
AA	1.3	1.0 2.0	8	18.5	4 40	10
IR	1.2	1.0 1.8	8	9.0	6 15	14
-MSH	1.2	1.0 1.9	14	5.7	2.9 21.5	14

Table II

References

Beitch B R and Eakins K E (1969) The effects of prostaglandins on the intraocular pressure of the rabbit Br J Pharmac 37 158-167

Bengtsson E (1975) The inhibiting effect of indomethacin on the disruption of the blood-aqueous barrier in the rabbit eye With a technical note by Krakau C E T and Öhman R Measurement of the aqueous flare Invest Ophthal 14 306-312

Butcher R W and Sutherland E W (1962) Adenosine 3 5 -phosphate in biological materials I Purification and properties of cyclic 3 5 -nucleotide phosphodiesterase and use of this enzyme to characterize adenosine 3 5 phosphate in human urine J Biol Chem 237 1244-1250

Puig-Parellada P Planas J M and Puig Muset P (1975) Imidazole inhibits the rise in intraocular pressure induced by arachidonic acid Ophthal Res 7 189-193

Waitzman M B (1970) Possible new concepts relating prostaglandins to various ocular functions Surv Ophthal 14 301-326

Waitzman M B and King C D (1967) Prostaglandin influences on intraocular pressure and pupil size Am J Physiol 212 329-334

Zink H A Podos S M and Becker B (1973) Inhibition by imidazole of the increase in intraocular pressure by topical prostaglandin E Nat New Biol 245 21-23

Zink H A Podos S M and Becker B (1975) Modification by imidazoles of ocular inflammatory and pressure responses Invest Ophthal 14 280-285

Poul Braendstrup

Report on Nordisk Oftalmologisk Centralkommitté (NOC)

Denmark Finland Norway and Sweden are each represented by two members in the NOC Now Iceland was invited to elect two members also

Mogens Norn

Report on Acta Ophthalmologica

The number of subscribers to Acta Ophthalmologica continues to rise

Mogens Norn who has just taken over the position as editor-in-chief expressed his gratitude to the retired editor-in-chief Poul Braendstrup and presented him a gift

Gunnar von Bahr

Report on Nordisk Oftalmologisk Litteratur-ring (NOLR)

It was decided that the NOLR should not continue in its original form A committee was elected to devise a new form

Gunnar von Bahr

Information about prevention of blindness

WHO has decided 1976 to be the year of prevention of blindness

Presentation of the K. K. K. Lundsgaard Medal

This medal is awarded to the author of the best paper in Acta Ophthalmologica since the previous Nordic Meeting. The committee in charge elected "Graft thickness after penetrating keratoplasty", Vol. 52, p. 893, written by Niels Ehlers.



Niels Ehlers, M.D.

Professor Braendstrup presented the K. K. K. Lundsgaard Medal in gold to Niels Ehlers.

Silver medals were presented to the retired editors of Acta Ophthalmologica: Gunnar von Bahr, Arne Huggert, Gosta Karpe, Hans Peter Petersen and Cote Osterlind.

Congressus XXIII ophthalmicorum septentrionalium

The Danish Ophthalmologic Society very kindly offered to host the next Nordic Meeting in Denmark in 1977.

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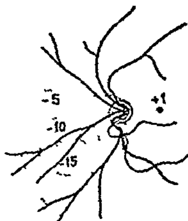
SUPPLEMENTUM 126

A K. K. K. LUNDSGAARD EDI COEPTA

The Nasal Fundus Ectasia

BY

Dag Riise



MUNKSGAARD COPENHAGEN 1975

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Acta Ophthalmologica
SUPPLEMENTUM 126

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CONTENTS

	Introduction	9
Chapter I	*Review of Literature*	
	Definition Criteria and Terminology	11
	Crescent	12
	Dysversion of the Optic Nervehead	15
	Ectasia of the Fundus	17
	Visual Acuity and Refraction	21
	Visual Field	24
	Other Findings	25
	Aetiology and Histology	26
	Genetics	30
Chapter II	*Clinical Investigations*	
	Collection of Material	31
	Methods of Examination	32
Chapter III	*Analysis of Clinical Material*	
	Occurrence	36
	Visual Acuity	39
	Refraction	41
	Astigmatism	42
	Ophthalmoscopy	43
	Visual Field	46
	Ectasia Depth Examination	47
	Other examinations	49
	Neurosurgical Examination	49
	Relations to other Ophthalmological Disorders	50
	Combinations with other Diseases	52

Chapter IV	Conclusions	53
Chapter V	Pedigrees	56
Chapter VI	Case Reports	59
Summary		99
Bibliography		102
Subject Index		107

The present studies were carried out during my work in the eye departments at *Århus Kommunehospital Rigshospitalet København* and *Københavns Kommunehospital*

It was my first teacher professor *Viggo A Jensen* who originally pointed out to me the possible connection between bitemporal hemianopia and inferior crescent

I wish to thank professor *Viggo A Jensen* professor *Holger Ehlers* professor *Poul Brændstrup* and professor *Børge Lawæt* for valuable advice stimulating interest and good working conditions

Help in locating case records in the neurosurgical department *Rigshospitalet København* made it possible to find several patients with the anomaly

I also owe many colleagues thanks for referring patients with nasal fundus ectasia especially *P H Madsen* for constructive criticism and *H Fledelius* for technical assistance in ultrasonography

Henry B Bilton translated the manuscript from Norwegian and Mrs *Gerd Holmlund* typed it I thank them for good collaboration

Last but not least my thanks go to all patients whose kindness and co operation have made this study possible

Hamar Norway March 1975

Dag Pise

This work originated in the discovery of a bitemporal hemianopia in a patient with inferior crescent myopia and astigmatism While seeking the cause of this I became interested in a clinical picture which while of common occurrence is relatively little known

The literature referring to the subject is comparatively sparse, and the terminology tends to be somewhat confusing thus I have felt it worthwhile to assemble the findings and diagnoses which in my opinion belong to a clinical picture

The starting point was ectasia of the fundus with the relative bitemporal visual field defect. Gradually however as I found more cases a clear picture was found of an anomaly involving the whole eye but principally localised in the posterior wall This discovery has not provoked any great modification in the objectives of the investigation which have been throughout to give a morphological description of the clinical picture Moreover emphasis has been given to explaining why visual field defects occur and how they may be distinguished from the bitemporal visual field defects found in disorders in the region of the optic chiasm

Certain special investigations such as ultrasonography refractometry and x ray examination are only taken into consideration in a few cases to clarify the picture Possible relation to other eye troubles or general diseases is des cribed

In some cases attempts have been made through family investigation to throw some light on the genetic factors involved These have mostly been restricted to the patients parents brothers and sisters and children In so far as the patients are found among subjects who have sought or been referred to eye examination and not in a routine investigation of the normal population it has only been possible to estimate the total incidence of this anomaly

It has been natural to adopt the monographic form since the size alone of the work will lead most readers to use it chiefly for summary reading and for reference when these cases are encountered

In reviewing the literature I have found it correct and most advantageous to use the individual author s own terminology and diagnoses The starting point in the individual works has varied widely Many have begun with the inferior crescent which is a common and conspicuous discovery for others

dysversion of the optic disc fundus ectasia or visual field defects have been the essential The result of this is that the selection of patients also is not the same among the individual authors even though in many cases they are coincidental In going through the literature emphasis has been given to some thorough works even though these do not take up the symptoms complex as a whole Some shorter notices which do not contribute anything new are omitted

Throughout my own material I have described something I regard as a complete picture but in going through the literature I have chosen to describe each individual finding in its own chapter

The discovery of an inferior crescent or inverse vessel emergence in the optic disc does not necessarily imply that the patient has the symptoms complex I have endeavoured to describe under the name the nasal fundus ectasia It is inevitable that throughout the literature patients will be mentioned who have individual symptoms but who strictly speaking lie outside the central theme To the extent this is possible these are only referred to in the chapters on the individual symptoms while they are omitted in the discussion of the collective picture This separation has resulted in some explanations and references being repeated in several sections this is done so that the individual sections may be read separately

My starting point has been the neuro ophthalmological aspect and this receives by far the most attention for the reason that in my opinion it is in that domain that the nasal fundus ectasia provokes the greatest practical difficulties in differential diagnosis

The visual field defects associated with the anomaly have led to several patients having undergone extensive examinations and some have even been operated for suspected pituitary tumor

If this work helps to elucidate these circumstances then its most important objective will have been achieved

CHAPTER 1

Review of Literature

DEFINITION CRITERIA AND TERMINOLOGY

As mentioned in the introduction it is evident from some of the literature and also from the investigation now presented that we have here an eye anomaly with a series of characteristic findings

The individual findings consist most often of an inferiornasal crescent dysversion of the optic disc with inverse vessel emergence nasal fundus ectasia with thinning of the sclera choroid and retina myopia astigmatism and relative temporal visual field defect

All of these symptoms are not necessarily present in every patient with the anomaly Since one is dealing with commonly occurring individual symptoms with a gradual approach to the normal there is no sharp natural line to define the presence of the anomaly The individual symptoms definition criteria and limits are discussed in the individual chapters

Some symptoms vary from one patient to the other both within families wherein several have the anomaly and between the two eyes in the same patient which entails using the total number of eyes rather than the total number of patients in the final analysis

The ectasia of the fundus and the consequent presence of the relative visual field defect have in my own work been decisive in my selection of patient material which is therefore not immediately comparable with several of the works to which I refer Many of the works mentioned even when they have taken another starting point include so much important and relevant information about the anomaly herein described that I found it natural to attach much importance to them in reviewing the literature The practical ophthalmological interest attaches chiefly to the fundus ectasia and the visual field defect this causes

On these grounds I have found that in the existing name jungle the term the nasal fundus ectasia was that which best covered the anomaly

Where the retina and the optic disc meet there is often seen a stripe of pigment called a choroidal ring In other cases is seen a thin whitish ring which can surround the normal optic disc This is called a scleral ring and may be developed into a half moon shaped segment at one side of the optic disc in which case it is then called a *crescent* (conus sichel croissant) The crescent arises because the choroid does not reach completely in to the optic disc in the defect the white scleral colour will shine through (Fig 1)

The crescent is of common occurrence but the reports vary somewhat In a large material of 32 000 eyes *von Szily* 1922 found that 25 % had crescent these were however patients who sought an ophthalmologist In a correspond ing school children material he found 11 % crescent which would suggest that crescent increases with age

The commonest form of crescent lies temporal to the optic disc and is seen especially in connection with myopia There is a clear preponderance of crescent in myopia The rather varying reports may be attributed to the absence of any clear transition between scleral ring and crescent

Vossius 1885 already separated the commonly occurring temporal crescent into a group by itself Crescent located otherwise has thus been assembled under the name heterotypical crescent (*von Szily* 1922 *Beeler* 1929 *Ziering* 1936) Other have also chosen to split up this group in accordance with the crescent s direction

In addition to classification by location crescent has been further subdivided into congenital and acquired (myopic and senile) (*Bonamour and Leopold* 1960)

The myopic crescent is whitish like sclera and is seen most often in the temporal position It develops with the myopia and increases with the years The optic disc is opening and vessels are drawn in the crescent s direction where ectasia or staphyloma are also visible Such staphyloma can be the cause of the traction and secondary crescent.

The senile crescent corresponds somewhat to the myopic being greyish white in colour and commencing on the temporal side and often spreading from there to form a ring around the entire optic disc. At the same time degene rative alterations in the retina may be often seen as retinal drusen

The congenital crescent is seen early and does not develop noticeably over the years It is half moon shaped evenly demarked and with a colour which differs little from the other optic disc tissue The optic disc is often diminished so that the disc and the crescent together do not amount to more than an ordinary optic disc (*Beeler* 1929 *Leopold* 1960) Usually the width of the crescent is from 1/8th to 1/2 of the optic disc s diameter and often embraces from 1/4 to 1/2 of the circumference

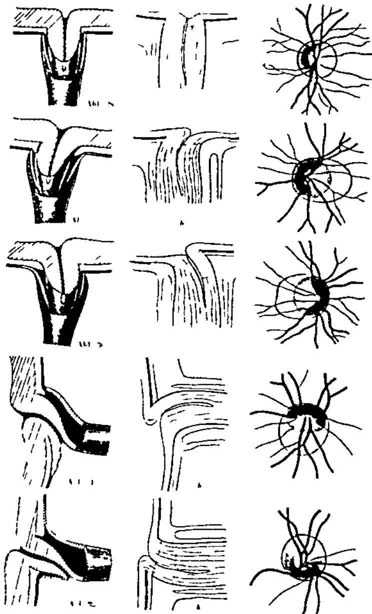


Fig 1
Crescent (A von Szily 19??)

After the main classifications I will pass on to discuss the *inferior and nasal crescent* which are the forms pertaining to the nasal ectasia of the fundus Since the superior crescent is extremely rare these forms will make up the greater part of the group "heterotypical crescent" which itself however amounts to less than 1/5th of the total cases of crescent (*Vossius* 1885 *von Sally* 1922)

Inferior and nasal crescent are described together since there is a gradual transition and the crescent is in many cases located in the inferior – nasal position. It should however be mentioned that *A Fuchs* 1947 has separated a form of nasal crescent from the inferior – nasal under the name inverse myopia" This distinction has not been upheld by others

There exists a fairly copious literature on the inferior crescent especially in German The first thorough review came when *E Fuchs* 1882 pointed out that the form and location of the inferior crescent distinguished itself from the myopic, temporal by its yellow white colour its sharp demarcation from the normal eyeground and by the absence of choroidal remains on the crescent In a review of 45 cases he showed the prevalence of myopia astigmatism anisometropia impaired vision and inverse vessel emergence Later investigations have to a large degree confirmed the results of that classic work It is however doubtful if the conjecture that the anomaly was of colobomatous nature can be sustained That supposition has led to the disorder often going under the name Fuchs coloboma

The following year *von Sally* (1883) supplemented these observations by calling attention to fundus ectasia located nasally to the optic disc. This has been described later by a series of authors *Ronne* (1916) measured the depth of the ectasia in dioptres *Beeler* (1929) found fundus ectasia in 70 % of the cases of heterotypical crescent He also pointed out that the width of the crescent increased with the degree of myopia and with age The crescent width in a 20 year old was rarely more than 1/8th to 1/4 of the optic disc diameter

Worton (1911) was the first to describe visual field defects in Fuchs coloboma He mentioned upper peripheral flattening for green targets *Fuchs* (1917)confirmed that finding but *Ronne* (1916) strangely enough describes normal visual field Many authors have later described bi temporal visual field defects (*Lohlein* 1934 *Ziering* 1936 *Rucker* 1946 *Walsh* 1957 *Berry* 1963 *Duke Elder* 1964 *Erney* 1964 *Ballentyne & Michaelson* 1970 *Graham* 1972 1973) That the visual field defects could disappear by correcting the eye with glasses corresponding to the bottom of the fundus ectasia was shown by *Schmidt* (1955) *Enokson* 1960 1965 *Bonamour & Leopold* (1960) *Kruse & Utermann* (1963) and *Pruse* (1966) Crescent is described together with pits of the optic disc by *Lauber* (1909) *Hoffmann* (1926) and *Edmund* (1930) and together with coloboma of the choroid by *von Sally* (1955) *Lohlein* (1934) has described one case of crescent and retinal detachment

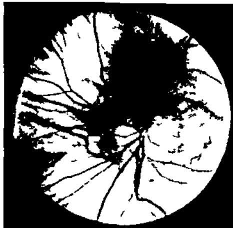


Fig 2

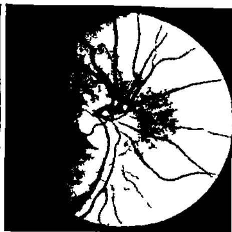


Fig 3

Fig 2 Left eye in case 57 Inferior crescent, Hypopigmentation and inverse vessel emergence.

Fig 3 Right eye in case 50 Inferior crescent and dysversion of the optic disc

Genetically inferior crescent was already reported to appear in families by *Fuchs* (1882) (2 brothers) *Vossius* (1885) (brothers sisters mother and child) *Hoffmann* (1926) (3 of 5 brothers and sisters) *Beeler* (1929) holds that the disorder is inherited like the anomalies of refraction and presumably in connection with corneal astigmatism he describes a case appearing in father and son *Bonamour & Leopold* (1960) describe the occurrence in a father and 3 children *Ida Mann* (1951) and *Waardenburg* (1968) hold that it is not possible to draw conclusions about the genetic factors from this evidence

DYSVERSION OF THE OPTIC NERVE HEAD

The appearance of the normal optic disc can vary within quite wide margins there being however a number of characteristic features

The physiological cup of the optic disc may be conceived as a cone or hemisphere with its base towards the inner eye and its apex in the direction of the optic nerve The axis of this cone shows the direction or version of the optic disc s cup

The vessels spread out fan like from the optic disc In many cases they will follow together in one direction before spreading out in the retina



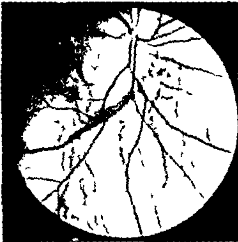


Fig 4 Fig 5

Fig 4 Dysversion of the optic disc case 1

Fig 5 Dysversion downwards with small disc and large inferior crescent ("gueule de four") case 36

The two things – the optic disc's cup and the vessels direction on emergence – will together establish the optic disc's "version The optic disc's normal version is slightly temporal which has its natural explanation in the fact that most of the vessels will go in the direction of the largest retinal region which also includes the macular area At the same time the optic nerve's axis is not vertical to the scleral coat but in the majority of cases directed slightly temporally (*Bonamour* 1968 *Duke Elder* 1964)

There will be a gradual transition from the normal optic disc to the optic disc with dysversion where the axis and the vessels point in another direction than temporal The term dysversion should therefore be reserved for the cases in which the tilt of the optic disc and the vessels emergence deviate clearly from the usual Dysversion must absolutely be accepted as a normal variation rather than a pathological condition The somewhat vague criteria mean that a decision as to the occurrence of dysversion depends to some extent on the investigator's judgement *Collier* (1957) arrived at a frequency of 8 % 80 % of all cases are bilateral *Bonamour* & *Leopold* (1960)

Morphologically the optic discs with dysversion besides the tilting and the direction of the vessels emergence are often characterised by a crescent margin in the direction of the dysversion Opposite to this is seen a slightly raised edge over which the vessels are bent in contrast to the straight vessels over the crescent Pale ectatic fundus in the sector of the dysversion is also common *von Sich* (1883) *Beeler* (1929)

The inferior nasal dysversion is the commonest form of dysversion *Leopold* (1960) The inferior is more rare and has often a special appearance in which the optic disc itself is reduced to a small half moon uppermost while the flat inferior crescent can exceed the optic disc in size (Fig 5)

That has in French literature been descriptively called gueule de four" Superior dysversion is extremely rare (*Leopold* 1960)

Associated anomalies may be cilic retinal arteries (*Collier* 1951) and ectopia of the macula (*Michel* 1959) Visual field defects are described by *Rucker* 1946 *Veirs* 1951 *Graham & Wakefield* 1973 *Manor* 1974

Since the optic disc turns in the opposite direction to the normal several authors understood it was rotated 180° on its axis and have used the expression *situs inversus* or *inversio papillae* (*Fuchs* 1882 *Elschnig* 1900)

The etiology is not clear Some take the anomaly to be an abnormal insertion of the optic stalk in the optic vesicle Traction and twisting of the tissue have also been suggested *Bedell* (1966) has seen inverted disc in connection with retinal folds arising after perforation *Brændstrup* (1969) describes a case arising after pre retinal hemorrhage in a newborn Finally several have as in the case of inferior crescent assumed the trouble to be an incomplete coloboma

ECTASIA OF THE FUNDUS

The posterior segment of the eye usually forms an approximately spherical surface There can occur however local developments and these are described under various names in the literature (scleral staphyloma ectasia of the fundus and *staphyloma posticum choroidea*) There is no doubt that several different types of ectasia can be found some of which have nothing to do with the symptoms complex described herein such as for example the contractile peripapillary staphyloma (*Wise Mac Lean & Gass* 1966 *Kral & Svarc* 1971) and posterior pole ectasia in high myopia In the case of the last mentioned it is however the location rather than the morphology which is the discriminating feature In the following notes will be described essentially those ectasias which lie nasal and below the optic disc and which nearly always occur together with inverse vessel emergence crescent and thinning of the retinal and choroideal pigment

Paulsen (1882) described staphyloma posticum choroidea with inferior crescent *Von Szily* (1883) gave one year later an excellent morphological description of the differences in the level which occur with inferior crescent The depth was measured by *Ronne* (1916) *Beeler* (1929) pointed out that 70 % of the patients with inferior crescent had ectasia of the fundus Other cases are



Fig 6
Ectasia of the fundus tilted disc and hypopigmentation

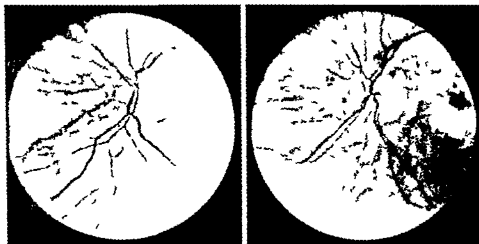


Fig
Ectasia I the fundus with degenerations Cases 26 and 61

described by *Fuchs* (1914) *von Sily* (1922) *Lohlein* (1934) *Buchlers* (1936) *Fuchs* (1947) *Lisch* (1949) *Badke* (1961) *Graham & Wakefield* (1973) and *Manor* (1974)

Andersen (1944) carried out quantitative perimetry with refractive errors and showed among other things a staphyloma visual field. He recommended that the visual field in these patients should be assessed with correction *Caccamise* (1954) reviews a case with visual field defect while *Schmidt* (1955) clearly accounts for the connection between visual field defects and ectasia He shows that the visual field defects can be eliminated by a correction of the eyes refraction corresponding to the floor of the ectasia Later *Enokson* (1960) *Bonamour & Leopold* (1960) *Kruse & Utermann* (1963) and *Pise* (1963) have given accounts of similar cases

Various methods have been employed to measure the ectasias depth Easiest and quickest has been to focus the ophthalmoscope sharply on the different areas of the retina Most observations are based on that Retinoscopy with sight in varying directions has been tried. *Ferree & Rand* (1933) with the help of a modified refractometer have been able to measure the retinal refraction They showed considerable variations also in the normal subjects and especially large retinal astigmatism peripherally One case with typical ectasia of the fundus is taken up wherein the centres was − 4 and the bottom of the *ectasia* − *9* dioptres

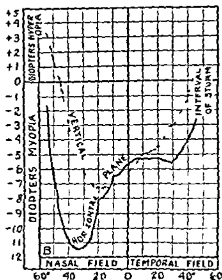


Fig 8

Refraction in fundusectasia (Frankenhauser and Enoch)

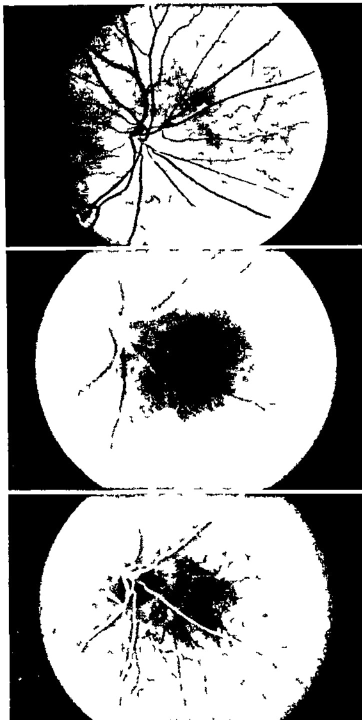


Fig 9

Right optic disc in a patient with nasal fundus ectasia Fluoresceinangiography shows choroidal vascular deficiency seen as a dark area corresponding to the ectasia both in the arterial and the venous phase

Frankenhauser & Enoch (1962) have measured with a Goldmann perimeter the lowest contrast threshold for a series of retinal points with varying refraction before the eye That refraction which in a single point gave the lowest contrast threshold and thereby the sharpest picture of the light target on the retina was designated the correct refraction In this way the variation in refraction in the different areas of the retina was found but the method is too time consuming for practical use (Fig 8)

François Goes & Yobbagyi (1967) have measured by ultrasonography that the eyeball diameter corresponding to a pronounced staphyloma was 6 mm longer than outside the staphyloma *Trier & Bohm* (1968) using B scan technique in a typical case of fundus ectasia with visual field defect have been able to exhibit a cross section of the staphyloma *Fledelius* (1970) has examined one of the patients (case 12) with ultrasonography and found an ectasia depth of 4 2 mm

From nearly all the above mentioned works it emerges that the ectasia of the fundus occurs together with inferior crescent dysversion of the optic disc hypopigmentation in the fundus ectasia impaired vision myopia and astigmatism One case of temporal fundus ectasia with binasal scotoma due to refraction is described by *Kommerell* (1909) in a 23 year old woman with myopia and astigmatism

Histological investigations in connection with fundus ectasia have produced description of thinning of sclera choroidea and retina *Elschnig 1903 Behse* 1908 *Tertsch* 1913 *Fuchs* 1917 and *Salzmann* 1941 The same can be seen ophthalmologically as a light fundus occasionally with myopic degenerations *von Szily* (1883) *Ronne* (1916) *von Szily* (1922) *Beeler* (1929) *von Szily* (1935) and *Kruse & Utermann* (1963) hold that these degenerations are progressive Using fluorescein angiography *Hoyt* has found in a dramatic way the choroidal vascular deficiency in the involved sector of the fundus"

VISUAL ACUITY AND REFRACTION

Already in the first notices about crescent it appeared that it was often associated with significantly impaired visual acuity (*Fuchs* 1882) *Vossius* (1885) found only slightly reduced vision It is not clear from Fuchs material if the astigmatism was corrected in all patients *Elschnig* (1900) based his assumptions on 481 patients who had impaired vision with best refraction Of these 75 were emmetropic 202 hypermetropic and 204 myopic 217 had crescent or Bindegewebesring"

The results in a few important works are shown below

Table 1
Incidence of impaired visual acuity

Sight	Fuchs 75 patients	Beeler 62 patients	Leopold 89 patients
0.25	8	12	11
–0.25 –0.67	54	38	49
0.67	13	12	29

From *Leopold's* (1960) material it emerged that the visual impairment was much more pronounced in the eyes in which the disorder was unilateral Pleoptic treatment had no effect on this amblyopia

A series of investigators had also found reduced visual acuity in nasal fundus ectasia but most frequently in the region 0.5–1.0 (*Ronne* 1916 *Buclers* 1936 *Rucker* 1946 *Caccamise* 1954 *Enolsen* 1960 *Berry* 1963 *Kruse & Utermann* 1963 *Ruse* 1966 *Odland* 1967 and *Manor* 1974)

Ziering (1882) is of the opinion that the visual impairment can be attributed only in part to the astigmatism since the degree of myopia and astigmatism is not so pronounced that it can account for the impaired vision *Fuchs* (1882) has explained the disorder as coloboma and maintained that the low visual acuity could be attributed to that *v on Szily* (1883) raised doubts about this

Beeler (1929) interprets the visual defects as an amblyopia *Bonamour* (1969) holds that the small vessels to the papillomacular bundle function badly with

Table 2
Incidence of astigmatism

	Fuchs 1882	Vossius 1885	v Szily 19[illegible]	Beeler 1929	Leopold 1960
Total	43	75	1118	62	83
Emmetropia	2	1		4	11
Hypermetropia		7		9	16
Myopia	34	28		49	56
Astigmatism	[illegible]	39	378	46	72

dysversion of the optic disc and these *minimal anatomical alterations* can account for the reduction in visual acuity

Kommerell (1969) has put forward the interesting and to my mind likely theory that the retina in these patients lies obliquely in relation to the incoming light The effect of this as explained by *Stiles & Crawford* (1933) will be to reduce the visual acuity

The first notices about inferior crescent showed that the majority of the patients were myopic and that a good many had astigmatism (*Fuchs* 1882 *von S ily* 1883 *Vossius* 1885 *von S ily* 1922 and *Beeler* 1929) Astigmatism and refraction anomalies are in most materials taken into account when they exceeded 1 dioptre

Vossius figures in the above table can not be directly compared to the others since his are given as refractive error anomalies or astigmatism according to which was dominant

The considerable preponderance of myopia and astigmatism among these patients is pointed out by a series of investigators *Ronne* 1930 *Rucker* 1946 *Fuchs* 1947 *Walsch* 1957 *Badke* 1961 *Ruse* 1966 *Bard* 1967 *Odland* 1967 *Bonamour Bregeat Bonnet & Juge* 1968 and *Manor* 1974 A series of case reports has also shown the same *Ronne* 1916 *Bucklers* 1936 *Lisch* 1949 *Caccamise* 1954 *Enokson* 1960 *and* 1965 *Berry* 1963 *Kruse & Utermann* 1963 *Kommerell* 1969

In contrast to this *Worton* (1911) also quoted by *Duke Elder* (1964) declares that hypermetropic astigmatism is the most frequent with inferior crescent *Duke Elder* however distinguishes between inferior crescent and dysversion and states that myopic astigmatism is the most frequent in the last named

That the refraction varies considerable in the fundus was already mentioned by *von S ily* (1883) measured by *Ronne* (1916) and very clearly demonstrated by *Leopold* (1960) *Fuchs* (1882) found anisometropia in 70 % of his material The degree of myopia is most often moderate The majority lie in the region of –1 0 to –5 0 (*Leopold* 1960) but degrees of up to –15 0 have been described

The astigmatism is often 2–4 (*Fuchs* 1882) but is to be seen over 5 dioptres (*Leopold 1960) Beeler (1929) states that 1–3 dioptres are the most usual and* occur in ,4 % of the eyes *Worton* (1911) has stated that the astigmatism corresponds to the crescent s direction The cylinder axis is said to be often irregular (*Bonamour & Leopold* 1960 *Bard* 196,) The finding of a corneal astigmatism which to some extent corresponds to the total astigmatism has been taken to indicate that the anomaly does not affect only the papillar region but involves the whole eye (*Fuchs* 1882 *Vossius* 1885 *Worton* 1911)

Von S ily (1922) has raised doubts about the widely held concept that *corneal astigmatism s frequency was abnormally high He found 33 % astigm*atism over 1 dioptre with heterotypical crescent and something similar in a

pituitary tumor growing laterally into the cavernous sinus Even though the visual field defects in ectasia of the fundus can often be distinguished from the defects due to chiasmal region tumors it is important to remember that the one disease does not preclude the other

Hoyt has moreover also observed that several patients with ectasia of the fundus had had amaurosis fugax in childhood and raises the interesting question if the ectasia of the fundus can be seen in connection with an ab normality behind the eye *Manor* (1974) describes a case with ophthalmoplegic migraine

Pits of the optic disc together with inferior crescent have been described by *Lauber* 1909 *Hoffmann* 1926 and *Edmund* 1930 Holes and degenerative changes in the macula are described together with dysversion in 4 cases by *Bonamour* 1964 and in 8 cases by *Didier Laurant* 1966

Too short space between the optic disc and macula is described by *A Fuchs* 1947 in inverse myopia while *Bonamour & Leopold* 1960 have on the con trary found too large a space between the optic disc and macula *Michel* 1959 and *Grondahl* 1963 have seen crescent in heterotopia of the macula

Dysversion and glaucoma are described by *Veirs* 1951 *Chadwick* 1965 *Graham & Wakefield* 1973 *and Manor* 1974 The cupping and the optic disc in Chadwick s case looks somewhat like a pit of the optic disc He reports in the same way as *Kestenbaum* 1961 and *Chandler & Grant* 1965 that the glaucomatous cupping in this case begins first inferiornasally in contrast to the usual temporal start The visual field defects in these cases begin tempor ally

In multiple sclerosis *Fuchs* 1947 has described how the pallor of the optic disc begins in such cases in the lower sector and not temporally

10% of the cases of inferior crescent in *Fuchs* material from 1882 had anisometropia and in some cases he found at the same time the presence of medullated nerve fibres

Retinal detachment is reported in one case by *Lohlein* 1934

AETIOLOGY AND HISTOLOGY

Amongst most authors there is agreement that nasal ectasia of the fundus with inferior crescent is a congenital anomaly in which crescent and ectasia can increase over the years but intense disagreement has prevailed as to the cause of the disorder There are practically as many suggestions as there are works and even though these concentrate on a few chief theories the problems are not finally solved

There exists a series of histological examinations and agreement reaches so far as to find an evident thinning of the sclera choroidea and retina in the ectasia of the fundus adjacent to the crescent Sal mann 1893 and 1941 Elschnig 1900 and 1903 Symens 1902 Behse 1908 Tertsch 1913 Fuchs 1917 von S ily 1922 Hoffmann 1926 Scheerer 1930

Traction has been emphasized as the cause of crescent staphyloma and dysversion of the optic disc. *Schnabel* 1874 held that crescent developed secondarily to the staphyloma with traction *Behse* 1908 held that crescent originated with atrophy of the choroid and subsequent wastage in the pigment epithelium upon traction and based this on histological investigation *Bedell* 1966 holds that inverted disc can arise after perforating injuries with secondary traction A similar case is shown by *Brændstrup* 1969 arising after vitreous haemorrhage in a new born

Finally *Paulsen* 1882 has observed that inferior crescent is found more often in seamen than in others and from this has drawn the fanciful conclusion that it must be due to traction since seamen look so much up at the heavens stars sail and mast

Torsion and wrong attachment of the optic nerve in the eyeball have been put forward as possible causes by *von S ily 1922 Beeler 1929 Fuchs 1941 and Sorsby 1964*

In a very comprehensive and thorough work *von S ily* 1922 has defined the disorder as a malformation in the papilla epithelialis primitiva The alterations in the mesodermal vessels sclera and choroid are secondary and *conditioned by the effect of disturbed development Ernyei* 1964 is on less sure groud in his suggestion that the disorder is due to defective development of the optic nerve fibre

Many clinical and histological works some quite fundamental have con cluded that inferior crescent must be understood as a form of coloboma *Fuchs* 1882 *Vossius* 1885 *Salt mann* 1893 *Tertsch* 1913 *Seefelder* 1921 *Beeler* 1929 *Scheerer* 1930 *Ziering* 1936 *Mollenbach* 1947 *Badke* 1961 *Waardenburg* 1961 *Kruse & Utermann* 1963 The grounds for this have been that the crescent *and the light ectatic region lie in a position corresponding to the eye s embryo* nic cleft and that the retina choroidea and sclera in that region are thinner than normal since however it is rarely a question of defects or duplication it is not total colobomas but weakness in the closure of the embryonic fissure

The simultaneous occurrence of coloboma and inferior crescent has also been used as an argument that the disorder was of colobomatous nature *Fuchs* 1882 reports 4 such cases but 3 of these are macular coloboma which can hardly be accepted as defects in the embryonic fissure Pictures of inferior crescent and coloboma are *however shown by Duke Elder 1964 and Bonamour & Leopold* 1960



Fig 10
Histology of inferior crescent (Elsching)

Vossius 1885 holds that inferior crescent is a rudimentary coloboma and regards the embryonic fissure as a locus minoris resistencia

After thorough histological studies *Elsching* 1900 asserted that only cases with ectasia of the fundus are of colobomatous nature but that it is not possible ophthalmologically to distinguish crescent from coloboma In a later work in 1903 he declared however that crescent as opposed to coloboma is not a malformation but an anomaly due to *incomplete development of the sclera*

The posterior part of the sclera contrary to the anterior develops first in the 5th foetal month *Ida Mann* 1957 If the posterior part continues to be thin it may be stretched into a staphyloma under the influence of the intra ocular pressure The pigment epithelium of the retina has a decisive influence on the growth of the sclera *Gruenwald* 1944 The low recording on the electro oculogram in ectasia together with the normal electroretinogram can be taken to indicate that the pigment epithelium is involved *Blach Jay & Mac Faul* 1965

Tertsch 1913 and *Mann* 1957 have sought the cause of inferior crescent in a development disturbance in the secondary eye vesicle They hold that the most probable cause must be a defective development of the pigment epithelium at the margin of the optic disc

The acceptance of ectasias of the fundus as a form of congenital myopia *Beeler* 1929 *Fuchs* 1947 makes it natural to imagine a similar etiology The symptoms of congenital myopia are given by *Hiatt Costenbader & Albert*

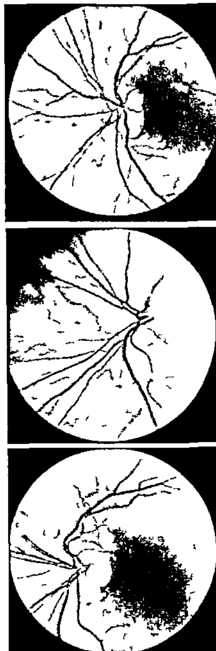


Fig 11

Left eye in 3 siblings with nasal ectasia of the fundus (case 41 45 and 47) 41 most crescent the others most dysversion

1965 to be scleral ectasia crescent dysversion choroidal mottling weak pig mentation and vitreous floaters These symptoms correspond very well indeed to the findings in ectasia of the nasal fundus

As regards the etiology of congenital myopia the same uncertainty prevails as with the ectasias of the fundus Family appearance occurs *Hiatt et al* Pre maturity is predisposing *Birge 1955 Fletcher & Branden* 1955 and toxemia of pregnancy has been present with more than normal frequency *Gardiner & James* 1960

GENETICS

The heredity of ectasia of the nasal fundus is not defined The reports are sparse and largely limited to case reports of occurrence in families

Beeler 1929 has stated that the disorder is inherited in a similar manner to myopia which does not go very far towards solving the problems since the hereditary nature of axial myopia is not known either

Goldschmidt 1968 states that the myopia which increases during growth is predominantly genetically determined with a polymeric mode of inheritance Very high myopia is a mixed group and the moderate late myopia is chiefly environmentally determined In congenital myopia *Hiatt Costenbader & Albert* 1965 point out the appearance in families

Reports on the family appearance of inferior crescent have been made by *Fuchs* 1882 (2 brothers) *Vossius* 1885 (brother and sister mother and child) *Hoffmann* 1926 (3 of 5 brothers and sisters) *Beeler* 1929 (father and son) and *Vogt* 1938 (uniovular twins)

As with crescent the reports on dysversion and heredity are limited to sporadic family cases *Leopold* 1960 has seen the anomaly in a father and 3 children and *Bonamour* 1968 quotes the same cases *Ernyei* 1964 declares without going into details that he does not believe the disorder to be here ditary

Ida Mann's 1957 conclusion that nothing definite can be said about the heredity of crescent but that it can hardly be recessive is about all that can be expressed today

Clinical Investigations

COLLECTION OF MATERIAL

The entire 66 patients with nasal fundus ectasia who are presented here were collected in the period 1965 to 1969 The majority have been encountered in *hospital work and especially in the ophthalmic clinics in Aarhus Municipal Hospital* the *University Hospital*s departments in *Blegdamsvej* and *Tagensvej* in København and in *København Municipal Hospital*

The first cases were found by routine perimetry in the neuro ophthalmological clinic As the clinical picture presented itself more clearly to me I found more cases by routine ophthalmoscopy Already the simultaneous discovery of astigmatism myopia and impaired vision can provoke suspicion that the anomaly is present Some cases have been referred to me from hospital colleagues who have shown a kind interest in the work

In 8 cases I have examined the patients nearest relatives limited to parents brothers and sisters and children Among these relatives were found 8 cases of fundus ectasia The result of these investigations is shown in Chapter V

In a search for more cases of fundus ectasia I undertook in 1968 an investigation of patients who had been admitted to the neurosurgical department of the University Hospital Tagensvej with bitemporal hemianopsia Among the 34 patients where there was not found any primary cause for the visual field defect it turned out that in 8 cases the explanation lay in nasal fundus ectasia (*Riise* 1970)

It has been a characteristic feature that the patients have not sought an ophthalmologist because of symptoms connected with the anomaly itself but that this has been observed in connection with examination of other eye disorders or general diseases A quite different result might have been obtained if the investigation had been undertaken in normal ophthalmic practice and not in hospital clinic It is therefore also clear that in the collected material merely because of the selection there will be a preponderance of other eye disorders and general diseases hardly having any connection with the eye anomaly

Anamnesis

Upon examination of patients with fundus ectasia notations were made on age sex and the reasons for seeking an ophthalmologist In order to get an idea of whether the disorder was stationary or progressive many were asked how old they were when they began to use glasses whether they saw badly and whether the strength of the glasses had been increased It was also noted whether the patients had other eye disorders or general diseases

Determination of refraction

Determination of visual acuity and refraction was performed chiefly by subjective methods on the first occasion most often with trial lenses and cross cylinder Corneal astigmatism was investigated in all cases with Schiotz – Javal ophthalmometer to get an idea as to what degree the frequently occurring astigmatism was of corneal origin After this streak retinoscopy was carried out and in some cases refractometry also All patients were examined both with and without cycloplegia

The fact that in nasal fundus ectasia even with the best correction visual acuity of 1 0 is often not achieved has led to thorough and repeated investigations to obtain the best result

Ophthalmoscopy

Ophthalmoscopy was performed in mydriasis Special attention was paid to the optic disc cupping vessel emergence direction and the presence of crescent The fundus was judged as to colour degeneration and atrophy Under the ophthalmoscopy the refraction in different parts of the fundus was judged special emphasis being given to the macular region and the bottom of the fundus ectasia The method used is similar to that used in estimation of papilloedema s prominence whereby the ophthalmoscopies adjusted to the most positive dioptrevalue with which each point in the retina can be sharply seen If the investigator is emmetropic and does not accommodate the approximate refraction can be read off in this way

In 74 of the 115 eyes a photographic registration was made of the optic disc and retina using Zeiss retina camera A difficulty in this is that sharp focus must be made on the optic disc the bottom of the ectasia or some other point since the differences in level make it impossible to see all parts sharply at the same time

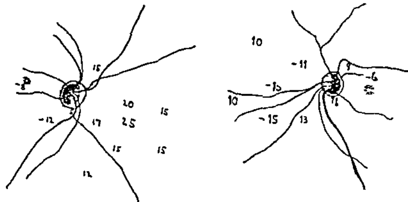


Fig 12
Determinations of the level differences in fundus by point ophthalmoscopy in a case of nasal ectasia of the fundus (case 21)

Perimetry

The visual field defects were first found by campimetry on Bjerrum Screen at a distance of 2 meters The target size varied but most often first tries were made with a 3 mm white object Later the visual field was examined in a Goldmann perimeter with varying target sizes

The primary investigations were performed without refraction thereafter with the patient s refraction and finally with a refraction between that of the bottom of the fundus ectasia and the patient s own refraction This last was done in order to establish to what degree the visual field defects were due to level differences in the fundus

With correction corresponding to the fundus ectasia there came in some

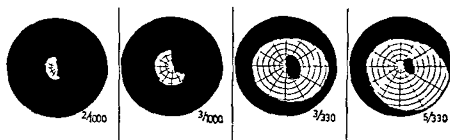


Fig 13
Perimetry of a relative visual field defect increasing target

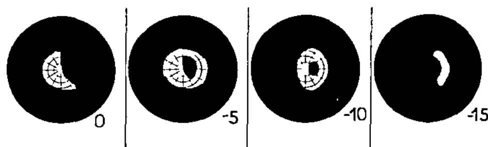


Fig 14
Perimetry of a refraction scotoma using different corrections

cases narrowing of the isoptres for the rest of the retina and it became neces sary after correction to find a new visual field target which restored the original isoptres The visual field defect was then controlled with that target

Retinoscopy and refractometry

In some cases attempts were made to determine the refraction of the individual retinal points by retinoscopy at determined angles from the visual axis Re fractometry was undertaken with the help of a coincidence refractometer (Zeiss Jena) Both methods showed refraction differences but since they were both less exact and more difficult to use than the simple ophthalmoscope method the results are not taken into account in this work

Ultrasonography

Measurement by ultrasound (a method) was performed in 2 cases with Kretz technik Model 7000 in order to judge to what extent the eye really was lengthened in the ectatic area One of these cases is earlier published as a case report (*Fledelius* 1970)

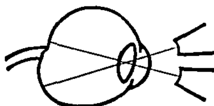


Fig 15
Ultrasound examination (Fledelius)

Electroretinography was performed in one single case where there was a suspicion of tapetoretinal degeneration In 3 of the cases with pronounced unilateral fundus ectasia x ray examinations were made of the orbits and optic foramina This was done in order to come to a decision about the possible presence of abnormalities or assymetry which could be related to the eye anomaly

Analysis of Clinical Material

OCCURRENCE

Nasal fundus ectasias are not sharply differentiated from the smaller level differences in the normal retina Since there are found transitional forms both the degree and localisation will be important for the diagnosis

The appearance of temporal visual field defects has however been the decisive factor in the selection Perimetry was performed with targets whose isoptres extended about 20° into the visual field It is precisely these visual field defects which are of the greatest interest in the usual clinical examina tion

The material consisting of 115 eyes in 66 patients comes chiefly from hospital clinics and departments Some were referred for visual field defects It is difficult therefore based on this material to draw any conclusion about incidence in the population as a whole

By examining 300 successive patients over 7 years of age in a general ophthalmic practice in Hamar in Norway I found 5 patients with nasal fundus ectasia and temporal visual field defects Since most of these patients are myopic with astigmatism they will presumably have been more likely than others to seek an ophthalmologist This could indicate that about 1–2 % of the population has the anomaly

Table 3
Survey of sex incidence

	Males	Females
Monolateral	8	9
Bilateral	21	28
Total	29	37

The moderate but not statistically significant preponderance of women in the material can be attributed to the circumstance demonstrated by *Jensen* 1963 and *Lorentzen* 1966 that women to a higher degree than men seek the ophthalmologist in Denmark. Since the question here is about an often fortuitosly revealed anomaly and not a disorder which necessarily leads the patient to the doctor it is reasonable that the material will contain a surplus of women

Table 4
Age at the time of examination

Age in years	Males	Females
< 20	3	3
20 – 40	11	17
40 – 60	11	15
> 60	4	
Total	29	37

Table 5
Reason for admission to eye examination

Eye diseases	30
General diseases	28
Examination of relatives	8
Total	66

The material as is obvious from table 7 is marked by examinations undertaken in eyeclinics which were engaged to a large extent in neuro ophthalmology

Table 6

Eye disorders leading to admission

Refraction control	15
Retinal detachment	4
Exophthalmos	2
Impaired vision	2
Eye strain	1
Hemeralopia	1
Optic disc atrophy	1
Choroiditis	1
Superior rectus paralysis	1
Squint	1
Conjunctivitis	1
Total	30

Table 7

General diseases leading to admission

Headache	8
Epilepsy	[illegible]
Hemicrania	2
Neurological disease	2
Meniere's syndrome	2
Diabetes	2
Polymyositis	1
Spinal meningeoma	1
Operated cerebral aneurysm	1
Trigeminal neuralgia	1
Cerebral concussion	1
Heart disease	1
Arterial hypertension	1
Total	28

Table 8

Visual acuity	Number of eyes
1.0	27
0.67	45
0.5	22
0.33	10
0.2	4
0.1	7
Total	115

From table 8 it appears that only 1/4 of the eyes have a visual acuity of 1.0. The largest group lies in the region 0.33 to 1.0 and has also reading vision. Only one eye had les than 0.1.

The question as to why the visual acuity is moderately reduced in these cases is discussed in the review of the literature. It will be apparent from later tables that there is a great preponderance of myopia and astigmatism which may be a contributing cause of the poorer vision. This is supported by

Table 9
Visual acuities in 49 subjects with bitemporal nasal fundus ectasia

0 dxt	0 sin	1.0	0.67	0.5	0.33	0.2	0.1
1.0		8	3	1			
0.67		4	11	3	1	1	1
0.5			3	3			
0.33				5	1		1
0.2			1				1
0.1			1				

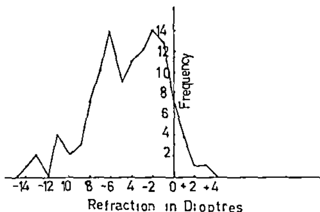


Fig 16
Curve of refraction in 115 eyes with ectasia of the fundus

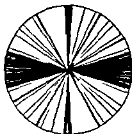
ASTIGMATISM

Table 13
Astigmatism in 115 eyes with nasal fundus ectasia

Dioptres	Monolateral cases	Bilateral cases	Total
0	3	13	16
0 5 – 0 75	3	14	17
1 0 – 1 75	6	36	42
2 0	5	35	40

The table shows that over 70 % of these eyes have an astigmatism of 1 dioptre or more Even though it was shown earlier that astigmatism increases with increasing degree of ametropia *Kronfeld & Denver* 1930 it is clear that the values lie far above what could be expected with corresponding refractive error in otherwise normal eyes The figures agree well with *Beeler* 1929 but are considerably higher than what *Szily* 1922 found in heterotypical crescent

There is no doubt that astigmatism must be regarded as part of the anomaly



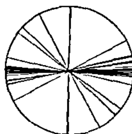


Fig 17

In figure 17 an attempt is made to illustrate the position of the negative cylinder axis A large accumulation is seen around 0° and some around 90 this applying to both large and small degrees of astigmatism In over half of the cases (59 eyes) the axis however deviates more than 5 from 0° to 90°

Corneal astigmatism agreed surprisingly well generally with total astigmatism both as regards degree and axis Where the visual acuity was better than 0 3 there were only 7 eyes in which the corneal cylinder axis deviated more than 10° and 9 eyes in which the corneal astigmatism deviated more than one dioptre from the total astigmatism

The fact that a somewhat conspicuous astigmatism is chiefly corneal points to the anomaly involving the whole eye and not only the posterior part where the ophthalmoscopical changes are seen

OPHTHALMOSCOPY

Ophthalmoscopy was performed on all patients under mydriasis In 74 of the 115 eyes the fundus also was photographed The examination was directed towards crescent, dysversion of the optic disc, inverse vessel emergence and ectasia of the fundus The definitions from chapter I are the basis for the findings

Crescent

By slight crescent are understood the cases where the crescent only makes an extra edge to the optic disc referred to sometimes in the literature as

Table 14
Incidence of crescent in 115 eyes

	Monolateral cases	Bilateral cases	Total
Inferior nasal crescent	11	53	64
Slight	3	27	30
Crescent in other direction	2	5	7

scleral ring 101 of 115 had traces of crescent Well over half 64 eyes had typical inferior nasal crescent (table 14) Since crescent is indeed ophthal moscopically a very striking symptom it is understandable that several have interpreted that as the essential in the anomaly

Dysversion

Table 15
Dysversion incidence in 115 eyes

Monolateral cases	Bilateral cases	Total
13	61	74

Table 15 shows that dysversion of the optic disc nasally and downward oc curred in well over half of the cases

Inverse vessel emergence

Table 16
Incidence of inverse vessel emergence

Monolateral cases	Bilateral cases	Total
14	83	97

Tilting of the optic disc and inverse vessel emergence occur mostly together In judging this the slighter cases are included many of which would have been described as normal in the usual ophthalmoscopy where no special attention was paid to the optic disc

Ectasia of the fundus

The existence of an ectasia of the fundus nasally and downward from the optic disc has been the essential element in selection of patients for perimetry and further examination It is therefore natural that a total of 107 out of 115 had ectasia deeper than 2 dioptres In most cases this was from 4 to 8 but in some cases 10 to 15 dioptres which means a 3 to 5 mm deep ectasy (see fig 18 page 47) The optic disc s refraction lay in many cases about midway between the macula and the bottom of the ectasia

Thinning of the retina and the choroid

In 106 eyes there was seen a light area corresponding to the fundus ectasia nasally and downward from the optic disc in which the choroidal vessels showed up distinctly In addition in 14 eyes were found degenerations which apart from their position resembled those seen in high myopia Degeneration was not found in patients under 30 years and 6 of the 11 patients with degeneration were over 60 years This indicates that degeneration in a similar way to high myopia develops with aging (fig 7 page 18)

2 of the patients with degenerations (cases 14 and 61) had been earlier interned in the ophthalmic department for treatment of choroiditis which from the description may well have been the development of the myopic degeneration

Table 17
Other ophthalmoscopical findings

	Case nr
Pigmented spots	13 and 45
Persistent hyaloid artery	18 and 39
Areolar choroideal sclerotic spot	45
Vitreous opacity	3
Medullated nerve fibres	43

These incidental ophthalmoscopic findings are considered as mere chance occurrences and can hardly have any connection with the anomaly

The visual field defects which were found had the following characteristics

1 The visual field defects were broadly speaking placed temporally and most pronounced in the upper temporal quadrant

2 The visual field defects were relative which means they diminished or disappeared when the target size was increased enough The targets which were used in the Goldmann perimeter to bring out the visual field defects are shown in table 18

Table 18
Target used in Goldmann s perimeter

	Relative intensity			
	4	3	2	1
Target 0	11			
Target I	20	24	42	3
Target II	11		4	
Target III	4			

As can be seen in the above table it was target 1 (1/4 mm) which in the majority of cases was best adapted to demonstration of the visual field defects as examination was made of isoptres in the region 20° – 30° By increasing the target size the defects gradually disappeared remaining longest as scotoma around the blind spot A typical example of this is shown in fig 13 page 33

3 Visual field defects were in most cases due to refractional differences That means that the defects were reduced or disappeared when corrective lenses were placed before the eye corresponding to the floor of the fundus ectasia

That the correction did not always remove the visual field defects implies that the retina in the area of the ectasia had reduced function

Since the retina seen with the ophthalmoscope was pale coloured in the ectasia region and in some cases with degenerations it is not surprising that visual function could be impaired

Several methods have been applied to determine the depth of the fundus ectasia *Retinoscopy* was tried in a few cases firstly of the macular region then of the region corresponding to the floor of the ectasia *Refractometry* of various areas of the fundus was also tried with a coincidence refractometer Zeiss Jena Both these methods proved usable but the examinations posed practical difficulties since the reflections were awkward to judge with a slanting axis of incidence Nor was it easy to localize exactly the bottom of the ectasia

The values obtained with retinoscopy and refractometry agree generally with those found by *reading off the ophthalmoscope s setting for a series of retinal points* The method with the ophthalmoscope was however much easier to carry out and the values could be reproduced with much more certainty for the simple reason that the individual points are easy to find again with the ophthalmoscope and the measurement rapid and simple The consequence is that the measurement of the ectasia in all patients in the material is performed with the ophthalmoscope which is held as closely to the eye as possible in order to reduce reading errors

As appears in the graph in fig 19 the highest incidence of fundus ectasia in that material has a depth of 4 to 10 dioptres but a few are even deeper

A sure method of judging the depth of a fundus ectasia is to measure by ultrasound the eye s length to the macula and to the bottom of the fundus

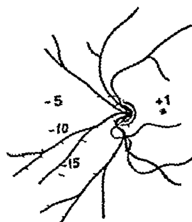


Fig 18

Case 1[a] examined in ophthalmoscope for estimating refraction in different retinal points

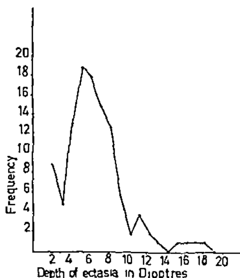


Fig 19

Shows the incidence classified according to the depth of the fundus ectasia

ectasia This is done in 2 of the patients in the material (cases 12 and 23) One of these cases is previously published (*Fledelius* 1970)

A problem with ultrasonic measurement is the difficulty of hitting exactly the bottom of the ectasia

Table 19
Result in case 12

Axis length	Macula	Ectasia
Right eye	22 5 mm	
Left eye	23 2 mm	27 4 mm

The ectasy in this case was monolateral in the left eye There is good agreement between the 15 dioptres level difference measured with the ophthal moscope and the ultrasonic measurement since roughly speaking 1 mm cor responds to 3 dioptres

Table 20
Result in case 23

Axis length	Macula	Ectasia
Right eye	24 3 mm	25.3 mm
Left eye	24 7 mm	26 2 mm

It would have been of special interest to have carried out beta scanning in these cases but the necessary apparatus was not available while the examina tion was in progress

OTHER EXAMINATIONS

X ray examination of the orbit was carried out in 3 cases (cases 10 12 and 24) with special pictures of the optic foramen to ascertain whether there was evidence of any osseous abnormality or asymmetry as the cause of the fundus ectasia The x ray examination showed a completely normal condition

Electroretinography was carried out in one case (case 66) The conditions were as expected normal as the electroretinogram represents the response of the total retina

NEUROSURGICAL EXAMINATION

Of the 66 patients in the material 9 had previously been interned in the neuro surgical department The reason in 7 of the cases (nos 10 16 17 19 23 39 and 64) was that bitemporal hemianopia had been found in the patients This had occurred when they had sought the ophthalmologist regarding headache, asthenopia or disturbed vision One patient (no 18) had had a transient polymyositis and one (no 20) had been previously operated for spinal menin geoma Both the 2 last mentioned patients as in the case of all the others were submitted to x ray examination of the cranium electro encephalography

carotis angiography and pneumo encephalography because there had been found bitemporal hemianopia

In spite of the x ray examination having given negative or uncertain results such importance was attributed to the discovery of visual field defects that 3 of the patients (nos 16 17 and 23) were subjected to exploratory craniotomy of the optic chiasm where the conditions were normal Bioscopic examination was made with chiasmal arachnoiditis in view and in 2 cases the histological answer describes thickened fibrous arachnoid

Since the visual field defects in these cases have been shown to be due to ocular causes it is quite probable that these are cases where the chiasmal arachnoiditis is used as an exclusion diagnosis because no other causes was found for the bitemporal field defects

The findings in 129 patients with bitemporal hemianopia in the neuro surgical department are reviewed in an earlier work (*Ruse* 1970)

RELATION TO OTHER OPHTHALMOLOGICAL DISORDERS

Besides the discoveries in the eye described as belonging to the nasal fundus ectasia and the more incidental ophthalmological discoveries there was found in the material a series of other eye disorders

Table 21
Ophthalmologic disorders in 66 cases with nasal fundus ectasia

Exophthalmos	6
Retinal detachment	4
Esotropia	2
Exotropia	1
Esophoria	1
Exophoria	1
Maculae cornea	1
Lens opacities	1
Pterygium	1
Xantelasma	1

Exophthalmos or protuberant eyes were seen in 6 patients (case 32 45 47, 54 59 64) Two of these had been referred for eye examination because of this finding The patients were quite aware that they had somewhat protruding eyes but none of them thought this had developed or increased since they became adults

Exophthalmometry showed in one of these cases 16 mm in both eyes The majority lay between 18 mm and 20 mm measured with Hertel s exophthalmo meter In only one case was found a difference of 1 mm between the two eyes *and in that case (case 54) the fundus ectasia was monolateral and the* prominence was greatest in the affected eye

As this is a question of long myopic eyes it is natural to connect the pro minence with the protuberant eyes found in high myopia In all these cases with exophthalmos the refraction in the bottom of the ectasia was between 10 and 20 dioptres It would appear from this to be the eyes length which makes them protuberant.

Retinal detachment was present in 4 of the 66 patients with nasal fundus ectasia (cases 9 47 50 5*i*) Two of the cases were bilateral but with an *interval of several years between the detachment in the two eyes* The total looks decidedly high even though the material is derived from eye depart ments which handled many cases of detachment All were referred to the department for their detachment and the nasal fundus ectasia was first noticed under ophthalmoscopy in the department Even if the total is too *small to serve as a basis for any statistical conclusion it is reasonable to suppose* that nasal fundus ectasia in like manner to other myopia increases the risk of detached retina It was of special interest to observe if the tears came specially in the region of the ectasia

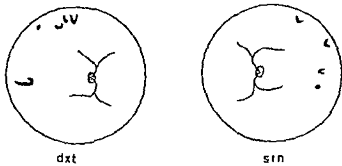


Fig °*0*
Shows the positions of the holes in 3 right and 3 left eyes with fundus ectasia and detached retina

As is seen in fig 20 the holes as is usual with detachment lie specially in the upper temporal quadrant No hole was found corresponding to the ectasia

After treatment the retina was attached in all these cases but in 2 cases the central vision was poor That is hardly grounds for believing that the prognosis for operation in these eyes differs much from that in cases without fundus ectasia

Strabismus

There were 3 evident cases of squint in the material along with 2 cases of large phoria Two cases were esotropia (cases 9 and 51) These had as had the case of large esophoria (case 3) monolateral fundus ectasia One case of exotropia (case 56) and one of exophoria (case 12) had bilateral fundus ectasia

That all patients with eso deviations had monolateral fundus ectasia indicates that the squint development has been secondary to the disorder or to the anisometropia which was present. The ectasia was found in the cases of esotropia in the squinting eye

A few discoveries of corneal macula lens opacities pterygium and xantelasma must be considered as incidental since these are usual disorders

COMBINATION WITH OTHER DISEASES

Since the patients are largely drawn from the hospital s departments the material tells very little about the combination of nasal fundus ectasia and other illnesses

The disorders which provoked the reference of the patients are given in tables 6 and 7 page 38 from which it is obvious many had neurological dis orders This must be seen in the light of many of the examinations being carried out in the neuro ophthalmological clinic Patients with headache diz ziness epilepsy and suchlike were routinely subjected to perimetry with small targets whereby the relative visual field defects were also revealed

Based on this material it is not possible to point to any connections between nasal fundus ectasia and general diseases

Conclusions

The present work propounds the existence of a characteristic eye anomaly which is here referred to as the nasal fundus ectasia"

The etiology of the disorder is not known Histologically there is found a thinning of the sclera choroid and retina localised nasally downwards from the optic disc The location which corresponds to the eye s embryonic cleft *has led many to interpret the anomaly as a form of coloboma The disorder* cannot however be a pure coloboma because there are no duplication or defects

Well founded suggestions that the disorder is due to a malformation in the papilla epithelialis primitiva or to a developmental disturbance in the secondary eye vesicle can not be dismissed What does seem clear is that the development must be seen in connection with the formation of the posterior part of the sclera in the 5th fetal month At this point the retina s pigment epithelium has been shown to have a decisive influence upon the growth of the sclera

The anomaly increases during the course of bodily growth but nothing is known about the effects of environmentally determined factors

Genetically the pedigrees (page 56) taken together with the literature show a family concentration Probably there is a polymeric mode of inheritance *similar to that of refraction anomalies*

Clinically the nasal fundus ectasia has a series of characteristics but does not in itself give any subjective symptoms What lead the patient most often to the ophthalmologist are problems with glasses in connection with myopia or astigmatism

The anomaly occurs in presumably about 1 – 2 % of the population with about equal incidence in men and women The condition must be regarded as congenital but progresses during bodily growth In 75 % of the patients the disorder is bilateral

Myopia is found in 90 % of the cases mostly in the range of 0 to – 8 diop tres

Astigmatism of more than 1 dioptre occurs in 70 % of the cases The majority have the negative cylinder axis in the vicinity of 0°

Visual acuity even with the best refraction is moderately reduced since only 25 % have visual acuity 1 0 the majority lying within the range 0 33 to 1 0 It is possible this is due to the Stiles Crawford effect as the retina stands obliquely in relation to the visual axis

The ophthalmoscopic picture contains a series of characteristic findings not all of which are necessarily present in all patients

In somewhat over half of the eyes in the material there was seen a distinct *inferior-nasal crescent* and the majority of the remainder had a scleral ring in the corresponding place

Tilting of the optic disc in a downward nasal direction occurred in 65 % of the eyes and a somewhat *nasally directed vessel emergence* in 80 %

The most characteristic feature was *ectasia of the fundus* lying nasally and a little downward from the optic disc The optic disc itself often lies within but not at the bottom of the ectasia The ectasia was most often 4 to 8 dioptres deep but could be up to 15 dioptres which corresponds to 5 mm In the ectasia the *fundus was light coloured* had *poor choroidal circulation* and *hypopigmentation* In some cases *degenerations* were seen most often in elderly patients

The most important alterations are localised in the eye s posterior part but the fact that the astigmatism to a large extent was corneal points to the anomaly involving the whole eye

The material gives no grounds to suppose that nasal fundus ectasia is a part of any general disease

Moderate *exophthalmos* is found in 5 % of the cases This corresponds presumably to the slightly protuberant eyes found in high myopia

Nasal fundus ectasia is found in 4 eyes in combination with *detached retina* The holes did not lie within the ectasia but in the upper temporal quadrant It is probable that the disorder similarly to other myopia predisposes to detachment

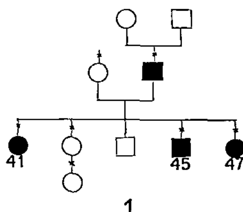
Monolateral fundus ectasia appears to predispose to *squint* and *amblyopia*

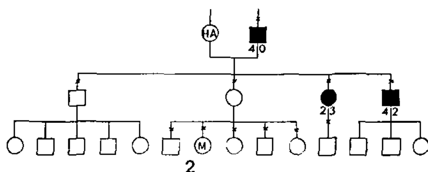
Familiarity with this anomaly is of the greatest practical interest because it involves bitemporal hemianopia which by mistake can suggest the visual field defects associated with tumours in the region of the optic chiasm

Three of the patients in the material had been subjected to exploratory craniotomy for suspected pituitary tumour and 6 others had undergone extensive investigation in the neurosurgical department Familiarity with the nasal fundus ectasia can spare these patients from very great inconvenience but it must not be forgotten that the combination pituitary tumour and nasal fundus ectasia can occur and has been described nor can this be surprising remembering that about 1 – 2 % of the population has fundus ectasia

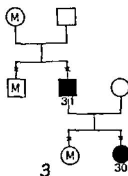
The most important investigation consists of perimetry of the patients with corrective glasses corresponding to the bottom of the fundus ectasia If the visual field defects then disappear they must be attributed to the fundus ectasia Perimetry alone with the eye s own refraction will in many cases reduce or remove the refractionally provoked scotomata In doubtful cases especially in the myopic perimetry should be performed with at the very least the patient s own glasses rather than without any correction at all

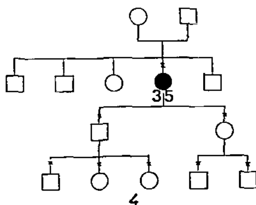
Pedigrees

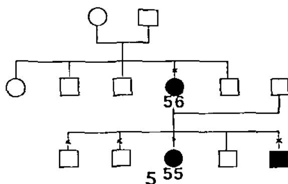




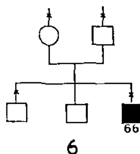
M – Myopia H – Hypermetropia A – Astigmatism
Numbers on figure refer to the case number

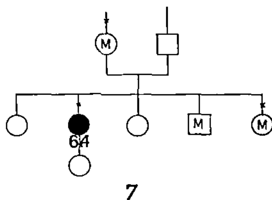


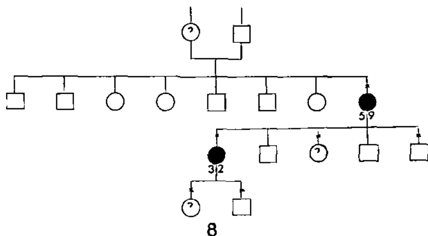




M – Myopia H – Hypermetropia A – Astigmatism
Numbers on figure refer to the case number







M – Myopia H – Hypermetropia A – Astigmatism
Numbers on figure refer to the case number

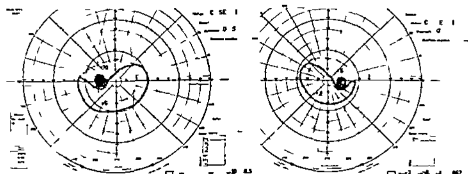
Case Reports

Case 1

A 19 year old woman (460212 E M L) with myopia and impaired vision for distance from childhood

Visual acuity	R E 06/ − 9.50 sph ⊃ − 0 50 cyl 110
	L E 0.50 − 6 00 sph ⊃ − 1 00 cyl 30

Ophthalmoscopy Both discs were tilted downwards with prominent upper edges Along the lower margin there was a very slight crescent formation. Below and nasally to the optic disc an ectasia of the fundus was found where the eyeground was seen most distinctly with −10 dioptres Corresponding to this the fundus was found to be a little lighter than the surroundings



Case 2

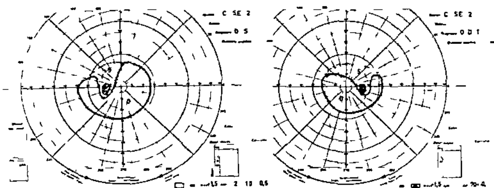
A 50 year old man (140474 P L S) with moderate hypertension without retinal changes

Visual acuity	R A 0 67 − 1 50 sph ⊃ − 1 00 cyl 1 0°
	L E 0 50 − 1 00 sph ⊃ − 2 00 cyl 10°

Ophthalmoscopy A clear inferior crescent in both optic discs

Below the optic disc a fundusectasia was found and correspond ng to this consider able retinal hypopigmentation

Perimetry Upper temporal defects in the visual field due to refraction anomalies

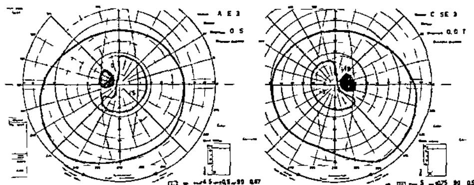


Case 3

A 69 year old woman (9ɔ0823 E M J) with slight esophoria No paralysis of the ocular muscles No somatic or neurological abnormalities

Visual acuity R E. 0 50 – 5 00 sph ⊃ – 0 75 cyl 90°
L E 0 6/ – 4 50 sph ⊃ – 0.ɔ0 cyl 90°

Ophthalmoscopy Both discs were slightly tilted with nasal vessel emergence and distinct nasal crescent The discs and the surrounding area were seen clearest with –10 dioptres while the macular area was seen most sharply with – 5 dioptres To the nasal side of the optic disc there was deficiency of pigment Ɪ erimetry with small targets revealed bitemporal incomplete hemianopia but the field defect disappeared on correction to the floor of the fundusectasia



Case 4

A ɔɔ year old woman (091007 K K E P) with corneal opacities after keratitis in child hood was examined because of headache after a cranial fracture

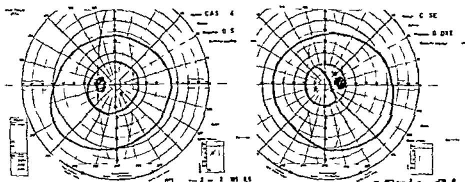
Visual acuity R E 0 4 – 2 00 sph ⊃ 1 00 cyl 170°
L E 0 ɔ – 2 00 sph ⊃ – 2 00 cyl 165°

Ophthalmoscopy R E The optic disc was tilted with downward nasal crescent The

temporal margin protruded 2 dioptres as compared with the nasal margin. Inverse vessel emergence was found with straight vessels nasally and bending vessels temporally To the nasal side of the optic disc the colour of the eyeground was pale, and the retina was seen most sharply with −10 dioptres

L.E The optic disc was slightly tilted with inverse vessel emergence otherwise normal conditions

Perimetry showed a temporal defect due to refraction anomalies on the right side normal conditions on the left side



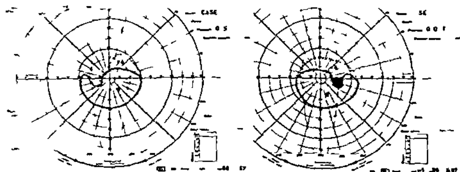
Case 5

A 45 year old woman (?00219 L H H) with post traumatic headache She had no ocular complaints and the neurological examination had not revealed any abnormalities

Visual acuity R E. 0 67 − 1 00 cyl 90°
L. E. 0 67 − 1 00 cyl 90°

Ophthalmoscopy The optic discs were slightly tilted with an indistinct inferior crescent Below the disc a small ectasia of 4 dioptres was seen, and sparse pigmentation of the fundus was seen in this area

Perimetry With small targets upper visual defects were disclosed The defects dis appeared completely in the right eye and partially in the left on correction correspond ing to the ectasia of the fundus



Case 6

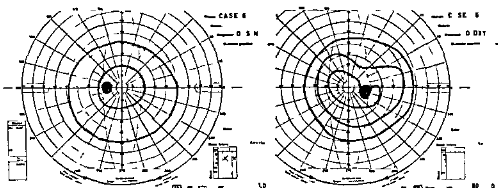
An 11 year old boy (540204 L W K) examined for epilepsy caused by head injury Neurological examination had shown no abnormalities

Visual acuity R E 1 0 – 1 00 sph ⊃ – 1 00 cyl 90°
L E 1 0 emmetropia

The position and movements of the eyes were normal

Ophthalmoscopy The right optic disc was slightly tilted with an indistinct crescent margin downwards Below the optic disc the fundus was seen most sharply with –5 dioptres and the retinal colour was light in this area The disc had a small central pitlike excavation Similar but less pronounced changes were found on the left side

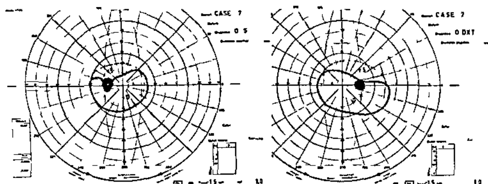
Perimetry On the right side there was an upper temporal field defect for small targets In addition to correction of the fundus ectasia it was necessary to increase the size of the target to make the defect in the visual field disappear Normal condition were found on the left side



Case 7

A 53 year old man (121111 K M A) was examined in the Department of Neurosurgery Århus Kommunehospital for epileptic seizures which had occurred at intervals of a few months for 3–4 years Neurological examination had disclosed normal conditions Pneumoencephalography showed slight central atrophy

Visual acuity of both eyes 1 0 – 1 50 sph



Ophthalmoscopy The optic discs were normal Below and to the nasal side of the disc an ectasia of the fundus of 5 dioptres was seen in both eyes Perimetry revealed upper temporal field defects which disappeared on correction corresponding to the floor of the fundus ectasia

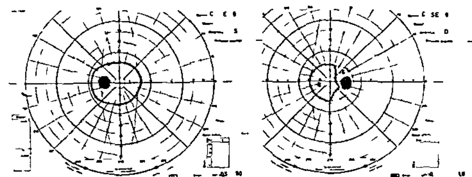
Case 8

A 90 year old man (441915 P R M) was admitted to the Department of Medicine Århus Kommunehospital after fainting fits of short duration Medical and neurological examinations did not reveal any abnormalities

Visual acuity 1 0 – 3 00 sph ⌓ – 0.50 cyl 90

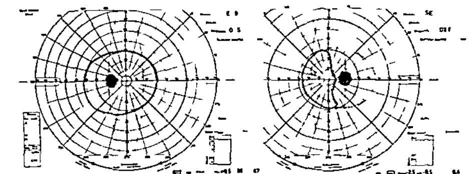
Ophthalmoscopy Both discs had a small crescent on the nasal side most distinct in the right eye. Around the disc there was a fundus ectasia in the right eye In this area the retina was seen most sharply with -6 dioptres

Perimetry with small targets revealed a temporal field defect on the right side which disappeared on correction with glasses corresponding to the bottom of the fundus ectasia In the left eye conditions were normal



Case 9

A 54 year old man (100810 J K.K.) had for 9 years been treated for trigeminal neuralgia He had 10 esotropia of the right eye



Case 13

A 20 year old man (480619 J L) was referred to Rigshospitalet in København for control of glasses in connection with military service

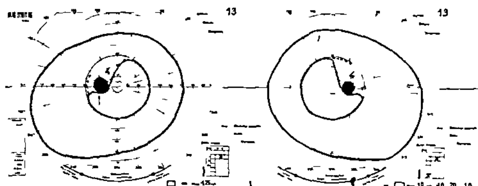
Mother and one sister are myopic The patient himself had used glasses since school age

Visual acuity R E 1 0 – 1 0 sph ⊃ – 1 0 cyl 20°
L E 1 0 – 1 25 sph

External examination position and eye movements normal

Ophthalmoscopy The discs were nasally tilted with inverse vessel emergence Some pigment on the upper temporal optic disc margin at the left side Pale fundus with 5 dioptres ectasia nasally downward from the optic discs

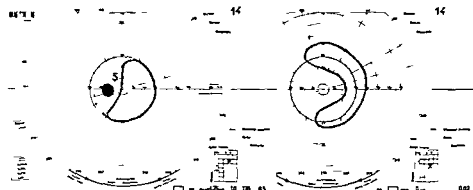
Perimetry showed bitemporal visual field defects due to refraction anomalies which disappeared on correction –4



Case 14

A 65 year old man (030519 A J) came to the eyedoctor in København because of difficulty in reading

He had in 1953 been interned for paracentral choroiditis At that time the visual acuity was found to be



Visual acuity R E 2/60 – 10 sph
L E 6/6 + 0 50 sph ⊂ – 1 0 cyl 40°

In the left centre there was seen a pale red area with pigment spots

The examination showed

Visual acuity R E 0 0? – 7 00 sph (was more myopic by retinoscopy)
L E 0 50 + 2 25 sph ⊂ – 1 0 cyl 45°

Ophthalmoscopy On the right side was seen peripapillar atrophy and considerable myopic degeneration in the centre On the left side the optic disc tilted nasally There was inverse vessel emergence nasal crescent and ectasia of the fundus with degeneration nasally from the disc The floor of the ectasia was seen sharply with –8 0 dioptres

Perimetry showed relative temporal field defect on the left side which disappeared on correction with –5 0 dioptres

Case 15

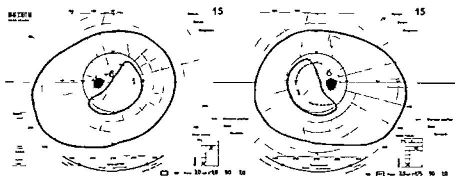
A 51 year old woman (170?03 L M B) was referred for eye examination from the neurological policlinic of Rigshospitalet København in connection with headache She had used glasses since childhood for nearsightedness with astigmatism.

Visual acuity R E 1 00 – 3 00 sph ⊂ – 1 75 cyl 90°
L E 1 00 – 3 00 sph ⊂ – 1 00 cyl 90

External examination position mobility pupils and corneal sensitivity normal

Ophthalmoscopy Inverse vessel emergence on the optic discs No tilt or crescent Ectasia nasally to both discs where the floor was most clearly seen with –10 dioptres

Perimetry showed relative superior bitemporal visual field defects which disappeared on correction with –6 0 dioptres



Case 16

A 22 year old man (450517 L O H) had used glasses for myopia and astigmatism since he was 6 years old and had since required stronger glasses

On control of glasses in connection with military service there was found a bitemporal hemianopia He was then interned in the neurosurgical department at Rigshospitalet København X rays of the cranium electro encephalography carotisangiography and pneumo encephalography showed normal conditions Nevertheless explorative cranio

5

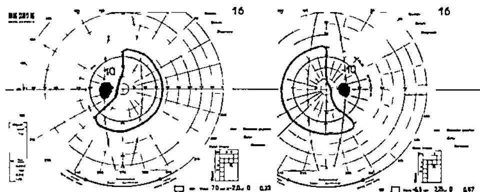
tomy was carried out with investigation of the chiasmatic region Apart from fibrious thickenning of the arachnoid nothing abnormal was found There were no complications No eye disorder in the family

Visual acuity R E 0 67 – 5 50 sph ⊃ – 2 25 cyl 0°
L E 0 33 – 7 00 sph ⊃ – 2 00 cyl 0°

Deepset small eyes Corneal diameter 11 mm

Ophthalmoscopy The discs were slightly tilted nasally with inverse vessel emergence and nasal crescent Ectasia around and especially nasally to the disc where the fundus was seen with –15 dioptres

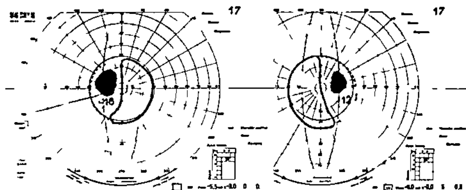
Perimetry showed relative bitemporal defect which disappeared on correction with –10 dioptres



Case 17

A 31 year old woman (340916 B P) had been myopic with astigmatism since child hood A sister was slightly nearsighted otherwise there was nothing in the family

In connection with headache the patient was examined by an eyedoctor in Randers in 1963 The discovery of bitemporal hemianopia led to the internment of the patient in the Neurosurgical department of Århus Kommunehospital X ray examination of the cranium electroencephalography carotisangiography and pneumoencephalography showed nothing abnormal Since repeated eye examination revealed bitemporal hemia



nopia an exploratory craniotomy was performed in Rigshospitalet København which showed only normal conditions apart from slightly thickened arachnoid The visual field defect was found to be unchanged on postoperative examinations Upon control examination in 1965 I found

Visual acuity R E 0 8 – 8 00 sph ⊃ – 2 00 cyl 5°
L E 0 8 – 5 00 sph ⊃ – 3 00 cyl 0°

Position mobility and pupils normal

Ophthalmoscopy The disc were nasally tilted with inverse vessel emergence Nasally there was a considerable ectasia of the fundus partly embracing the optic discs but especially the region lying nasally from these The floor of the ectasia was pale and was seen on the right side with –25 and on the left side with –15 dioptres

Perimetry showed bitemporal visual field defects which disappeared with correction corresponding to the floor of the ectasia

Case 18

A 57 year old man (100626 A W M N) began using glasses for myopia when aged 20 Several cases of myopia in the family In 1960 the patient was interned in the neuro logical department Rigshospitalet in København for polymyositis with a transitory uni lateral paresis of the oculomotor nerve On examination in the eye department there was found a bitemporal relative hemianopia especially upward X ray of the cranium and carotisangiography showed nothing abnormal No satisfactory explanation was found for the hemianopia which remained unchanged in the following years The symp toms of polymyositis disappeared

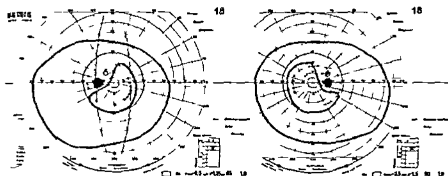
Examination in 1968

Visual acuity R E 1 0 – 3 50 sph ⊃ – 1 5 cyl 90°
L E 1 0 – 3 00 sph ⊃ – 1 25 cyl 65°

Appearance position mobility normal

Ophthalmo copy Optic discs widely physiologically cupped with indication of crescent margin distinctly inverse vessel emergence on both sides Ectasia involving the discs and especially the region lying nasally to them No atrophies A persistent hyaloid artery was seen on both sides The floor of the ectasia was seen with –19 dioptres

Perimetry showed relative upper bitemporal hemianopia which disappeared on correc tion with –6 dioptres



Case 19

A 64 year old man (041214 V C L) No eye disorders in the family The patient was examined in 1964 in the neurological department Rigshospitalet Kobenhavn for attacks of headache Eye examination revealed bitemporal hemianopia but otherwise normal conditions The patient was observed for possible pituitary tumour X ray examination of the cranium and pneumoencephalography showed normal conditions

In later controls in the eye department of Rigshospitalet the visual field defect was *found to be unchanged*

The headache had diminished

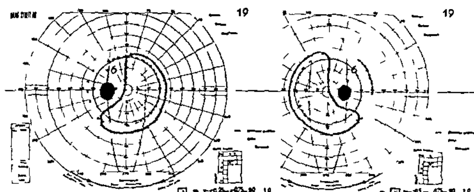
On examination in 1968 I found

Visual acuity R E 1 0 – 0 50 sph ⊃ – 0 75 cyl 90°
L E 1 0 – 0 25 sph ⊃ – 0 75 cyl 90°

Position mobility and pupils normal

Ophthalmoscopy Slightly nasally tilted discs with inverse vessel emergence Suggestion of crescent formation nasally Considerable fundus ectasia nasally from the discs where the floor was seen with –11 dioptres The retina was pale and thin in the region of the ectasia There were no atrophies

Perimetry showed relative bitemporal hemianopia which disappeared with correction of –6 and with use of large targets



Case 20

A 77 year old woman (910193 E J A) was operated for spinal meningeoma in the neurosurgical department Rigshospitalet Kobenhavn At a later internment for control examination in the eye clinic revealed visual field defect on the right side X ray examination of the cranium electroencephalography carotisangiography and pneumo encephalography showed nothing abnormal Later controls have shown no change in the visual field defect

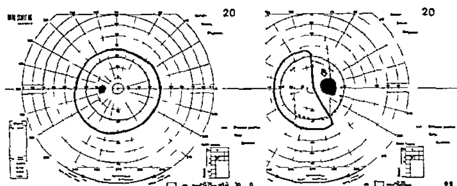
On examination in 1968 in connection with investigation of patients with temporal visual field defects I found

Visual acuity R E 0 8 – 2 25 sph
L E 0 8 + 1 75 sph ⊃ – 1 0 cyl 90°

Ophthalmoscopy The right optic disc had inverse vessel emergence slight nasal tilt and indication of crescent margin Nasally to the disc there was ectasia of the fundus

where the floor was pale and was most sharply seen with −10 dioptres On the left side the vessels were nasally directed on the disc otherwise conditions were normal

Perimetry showed relative temporal hemianopia on the right side which disappeared on correction with −8 and with large targets



Case 21

A 72 year old woman (94100? A A) had had a couple of epileptic attacks in connection with which fenytoin medication had been commenced As the patient complained of itching in the eyes she was referred to the eye clinic at Kommunehospitalet København

She had always seen badly with the right eye but did not use distance glasses No eye disorders in the family

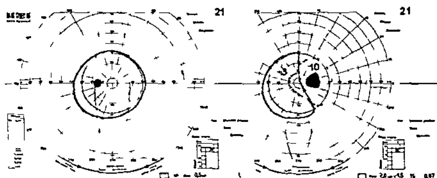
Visual acuity R E 0 67 − 2 0 sph ⊂ − 1.5 cyl 15°
L E 1 00 + 0 5 sph

Conjunctiva and cornea normal

Position and movements normal No exophthalmus

Ophthalmoscopy The right disc nasally tilted with nasal crescent inverse vessel emergence and ectasia of the fundus The floor was seen with −10 dioptres In the left eye conditions were normal

Perimetry showed temporal visual field defects in the right eye which disappeared on correction with −10 while the other limits contracted No defects on the left side



Case 22

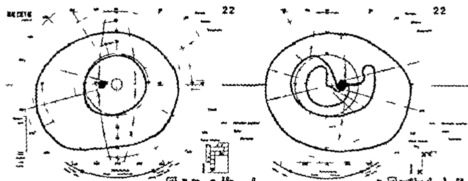
A 30 year old woman (3?0712 D C A) was interned in the neurological department at Århus Kommunehospital for hemicrania and came for routine eye examination There were no complaints about sight

Visual acuity R E 0 8 – 0 5 sph ⊃ – 3 5 cyl 5°
L E 1 0 – 2 0 cyl 5°

Position and mobility normal No ptosis or nystagmus

Ophthalmoscopy Well defined optic discs On the right side nasally downwards from the optic disc there was a small crescent The retina in the region around this was pale with a fundus ectasia of only 2 dioptres

Perimetry showed upper temporal visual field defect on the right side This remained unchanged with other refraction and barely noticeably changed with increasing target size



Case 23

A 39 year old woman (290521 E K A) had seen poorly since childhood but only began using glasses when aged 15

Family background see Pedigree No 1

In 1965 the patient consulted an eye doctor for eye strain and because a bitemporal hemianopia was found the patient was referred to Rigshospitalet København where bitemporal visual field defects were also found and the patient was then interned in the neurosurgical department X ray of the cranium electroencephalography and carotis angiography showed normal conditions Two attempts at pneumoencephalography failed Craniotomy with exploration of chiasma and optic nerves showed only normal conditions Later checks showed unchanged visual field

On examination in 1968

Visual acuity R E 0 67 – 7 0 sph ⊃ – 2 0 cyl 120°
L E 0 67 – 6 5 sph ⊃ – 2 0 cyl 60°

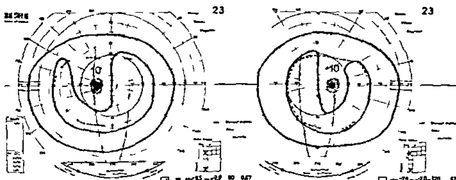
External examination position and mobility normal

Ophthalmoscopy The optic discs had slight crescent on the right temporally down wards On the left pointing downwards The vessels were slightly nasally directed Obvious ectasia of the fundus nasally to the discs with a pale floor which was clearly seen with –15 as compared with the macula s –8 dioptres

Perimetry showed bitemporal defects which disappeared on correction with −10
Ultrasonic examination

R centrally 24 3 mm ectasia 26 3 mm

L centrally 24 7 mm ectasia 26 2 mm



Case 24

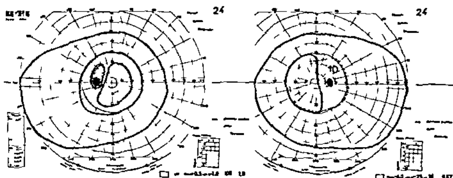
A 26 year old man (410128 K A) was referred to the eye department Rigshospitalet København because in a routine examination during military service he was found to have impaired sight No eye disorders in the family The patient had never had glasses

Visual acuity R E 0 67 − 4 0 sph ⊃ − 2 0 cyl 10°
L E 1 00 + 0.5 sph ⊃ − 1 0 cyl 100°

Position mobility normal no exophthalmus

Ophthalmoscopy The optic discs were nasally tilted with inverse vessel emergence and ectasia with loss of pigmentation nasally to the disc The floor was seen with −?0 on the right side and −6 0 on the left side

Perimetry showed bitemporal visual field defects which disappeared on increasing target size and by correction with −10 on the right side where the defect was most pronounced



Case 25

A 20 year old man (481123 T A) was examined during general practice when he came to the eyedoctor for control of glasses

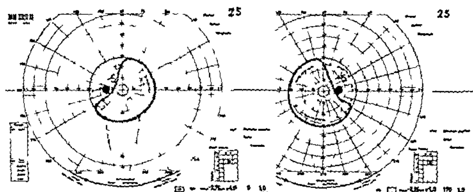
He had been myopic with astigmatism since early school years No other eye disorders

Visual acuity R E 1 0 – 2 95 sph ○ – 1 0 cyl 170°
L E 1 0 – 2 75 sph ○ – 1 0 cyl 0°

External examination position and mobility normal

Ophthalmoscopy Both optic discs nasally tilted with inverse vessel emergence Nasally to the disc was seen a pale ectasia of the fundus where the floor was most clearly seen with –7 dioptres

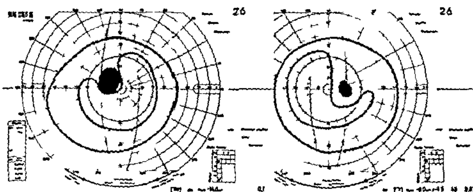
Perimetry showed bitemporal visual field defect for small targets which disappeared on correction with –5 dioptres



Case 26

A 34 year old woman (360620 T M B) was referred to the eye doctor in København because a dark spot had come and sight was failing in the left eye The patient had been shortsighted since childhood and had glasses when 6 years old Later she had several times got glasses of increasing strength

Visual acuity R E 0 67 – 9 0 sph ○ – 1 5 cyl 45°
L E 0 10 – 14 0 sph



Ophthalmoscopy On both sides was seen an inferior crescent and ectasia of the fundus nasally downward with degenerations in the region of the ectasia On the right side degenerations were found also in the macula region

Perimetry showed relative scotomata temporally upwards which did not completely disappear with correction

Case 27

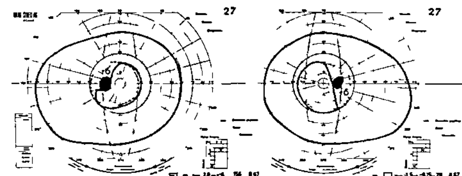
A 64 year old woman (010601 I B) had been previously operated for condrosarcoma of the right fibula In connection with a control she was referred to the eye clinic Århus Kommunehospital since there had occurred some headache and dizziness

She had herself obtained glasses for astigmatism when aged 20 The mother and a son were myopic with astigmatism

Visual acuity R E 0 67 – 1.5 sph ⊃ – 0 75 cyl 90°
L E 0 6 – 2 0 sph ⊃ – 0.50 cyl 155°

Ophthalmoscopy On both optic discs there was a nasal crescent and outside of this an obvious ectasia where the floor was pale with clearly seen choroidal vessels Corresponding to the floor of this the retina was seen with –8 dioptres in the ophthalmoscope

Perimetry showed relative upper bitemporal hemianopia which disappeared on correction with –6 dioptres



Case 28

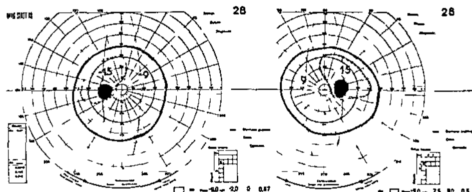
A 37 year old man (280490 F V C) had been operated several years earlier for an aneurysm of the right middle cerebral artery He was seen in connection with a control in the eye clinic Århus Kommunehospital

Visual acuity R E 0 5 – 9 0 sph ⊃ – 2.5 cyl 90°
L E 0 67 – 10 0 sph ⊃ – 2 0 cyl 0

Position mobility normal no exophthalmus or ptosis Pupil condition normal

Ophthalmoscopy The optic disc had lower nasal crescent and inverse vessel emergence Nasally downwards from and embracing the discs was an ectasia of the fundus where the bottom was most clearly seen with –18 dioptres

Perimetry showed relative visual field defect corresponding to the ectasia of the fundus which disappeared on correction with –15 dioptres



Case 29

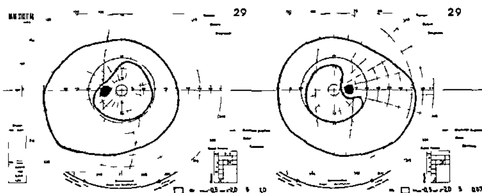
A 32 year old man (341227 P J C) was referred to the eye clinic Århus Kommune hospital in connection with hemicrania No earlier eye disorders

Visual acuity R E 0 67 – 0 5 sph ⊂ – 2 0 cyl 5°
L E 1 0 – 0 5 sph ⊂ – 2 0 cyl 5°

Appearance, po ition mobility normal

Ophthalmoscopy The right optic disc had inverse vessel emergence and a small nasal crescent margin There were similar but less conspicuous conditions on the left side There was a small ectasia of the fundus nasally to the disc where the bottom was seen with –4 dioptres

Perimetry A small bitemporal visual field defect which disappeared with larger targets but not completely with correction



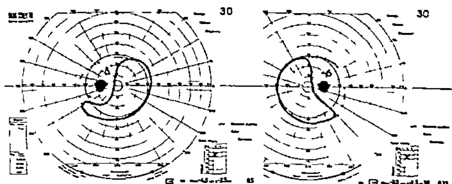
Case 30

A 11 year old girl (551208 J D) seen in normal practice when she came for control of glasses The father had a similar disorder (no 31) see Pedigree No 3

Visual acuity R E 0 33 – 3 0 sph ⊂ – 2 5 cyl 10°
L E 0 50 – 4 0 sph ⊂ – 2.5 cyl 0°

Binocular sight 0 67

Ophthalmoscopy Inverse vessel emergence on both optic discs Nasally to the optic discs ectasia of the fundus where the bottom was seen sharply with –10 dioptres



Case 31

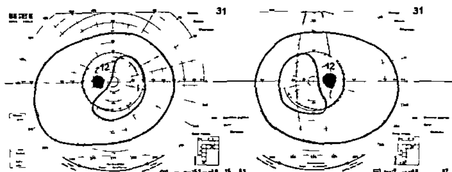
A 50 year old man (180 08 S D) was seen in normal practice in connection with family investigation The daughter (no 30) had a similar disorder (Pedigree No 3)

Visual acuity R E 0 6/ – / 0 sph ⊂ – 1 0 cyl 180
L E 0.50 – 5.5 sph ⊂ – 1 0 cyl 15°

Position and mobility normal

Ophthalmoscopy The optic discs had a crescent and slightly nasally directed vessel emergence Large ectasia of the fundus with pale bottom nasally to the discs The bottom of the ectasia was seen sharply with –15 to –20 dioptres

Perimetry Bitemporal relative visual field defects which disappeared on correction with –12 dioptres and with large targets



Case 32

A 34 year old woman (330825 H D) was examined in connection with a family investigation. Daughter of patient no 59 see pedigree no 8

Had seen poorly since childhood and already during schooldays was teased because she had prominent eyes coweyes

In 1942 the patient was examined at Rigshospitalet in København where there was found a refraction both eyes – 3 0 sph ⊂ – 2 0 cyl 0°

Exophthalmus was described

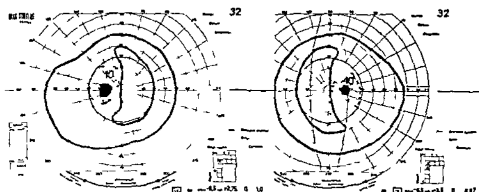
On examination of the patient in 1967 I found

Visual acuity R E 0 67 – 6 5 sph ⊂ – 3 50 cyl 0°
L E 1 00 – 6 5 sph ⊂ – 2 75 cyl 0°

Prominent eyes Exophthalmometry 19 5 mm – 19 5 mm/97

Ophthalmoscopy The optic discs tilted somewhat nasally downwards with a small inferior crescent margin and inverse vessel emergence Nasally to the disc was seen a pale ectasia of the fundus where the bottom was seen with –15 dioptres

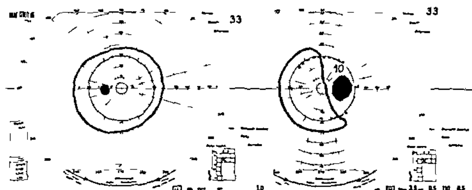
Perimetry Relative bitemporal visual field defects On correction with –10 dioptres some of the visual field defects disappeared



Case 33

A 36 year old man (301029 S F) As a child had similar sight in both eyes but later a right sided myopia had gradually developed He came to a practising eye doctor to have his glasses controlled

Visual acuity R E 0 5 – 3 5 sph ⊂ – 0 5 cyl 110°
L E 1 0 emmetropic



Ophthalmoscopy On the right side the optic disc was tilted nasally downwards with inverse vessel emergence and a wide inferior crescent Below and nasally to the optic disc there was an ectasia of the fundus the bottom of which was seen sharply with −15 dioptres A few myopic degenerations below and nasally to the optic disc The conditions on the left side were normal

Perimetry showed temporal defects on the right side which disappeared with larger targets and correction with −10 dioptres

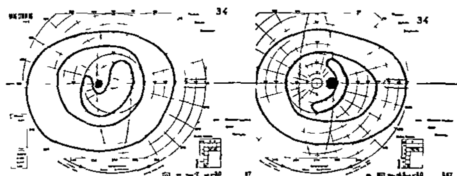
Case 34

A 43 year old woman (220303 L A G F) was interned in 1965 in the neurological department Århus Kommunehospital for epilepsy 6 of 9 brothers and sisters used glasses for myopia though none so strong as the patient The patient was referred to the eye clinic for routine examination where the findings were

Visual acuity R E 0 67 − 4 5 sph ⊂ − 3 0 cyl 0°
L E 0 67 − 7 0 sph ⊂ − 3 0 cyl 0°

Ophthalmoscopy The optic discs tilted nasally downwards with a half optic disc diameter wide crescent margin in the same direction The fundus pigmentation was scanty around the crescent and there was an ectasia the bottom of which was seen with −19 dioptres There was inverse vessel emergence on both sides

Perimetry showed superior temporal visual field defects on the left side while on the right side small targets produced only a bow temporally With large targets the visual field was normal



Case 35

A 68 year old woman (980517 A L M P G) was referred to the eye clinic Rigshospitalet København because after a frontal resection for sinusitis she had developed paralysis of the superior rectus muscle The paralysis subsided in the course of some weeks

The patient had been near sighted since childhood

Visual acuity R E 0 5 − 4 0 sph
L E 0 5 − 3 0 sph ⊂ − 1 0 cyl 100

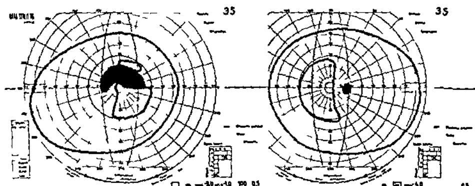
A hint of sub capsular lens opacification on both sides

Ophthalmoscopy Pale optic discs with large inferior nasal crescent Ectasia of the

fundus around the crescent where the bottom was seen with −12 dioptres The fundus was pale in that region with moderate degenerations Specially conspicuous degenerations on the optic disc at the left side probably explain some of the visual field defect here

Ocular pressure both eyes 15 mm appl

Perimetry showed bitemporal visual field defects *together with an arc scotoma on the left eye*



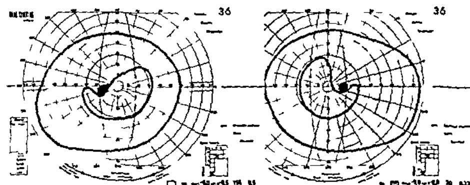
Case 36

A 59 year old woman (030414 A E K E H) had been short sighted since school age but was not aware of other cases of shortsightedness in the family She was referred to the eye clinic at Rigshospitalet in København for control of sight

Visual acuity R E 0 33 − 7 0 sph ⊃ − 2 0 cyl 30°
L E 0 50 − 6 0 sph ⊃ − 0 5 cyl 155°

Ophthalmoscopy The optic discs tilted nasally with inferior crescent which was specially wide on the right side Nasally downwards there was ectasia of the fundus where the retina was pale with distinct choroidal vessels The bottom of this was seen most sharply with −12 dioptres

Perimetry showed superior temporal visual field defects for small targets which disappeared on use of larger targets



Case 37

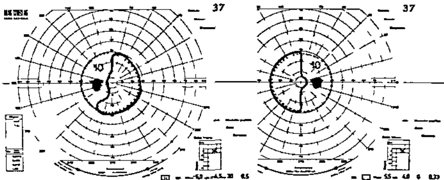
A 52 year old woman (150211 E M H) was under observation for organic brain disease and in connection with this was referred to the eye clinic Gentofte Amtsygehus No eye complaints

Visual acuity	R E 0 33 − 5 5 sph ⊃ − 4 0 cyl 0
	L E 0 50 − 5 0 sph ⊃ − 4.5 cyl 30°

Appearance position mobility and pupils normal.

Ophthalmoscopy The optic discs were nasally tilted with a small crescent margin Nasally to the optic disc was seen a pale ectasia of the fundus

Perimetry showed bitemporal visual field defect which disappeared with large targets and with correction of −10 dioptres

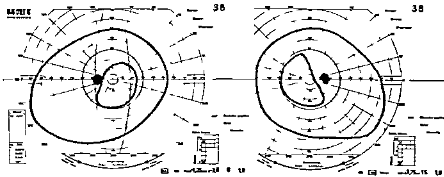


Case 38

A 59 year old man (080703) H G H) was interned in the medical department of Rigs hospitalet København for a heart disease and during his stay in hospital he was referred to the eye clinic

Visual acuity	R E. 1 0 − 3 75 cyl 15°
	L E 1 0 − 1 25 sph ⊃ − 3 00 cyl 0

Ophthalmoscopy Small inferior nasal crescent most distinct on the right optic d sc The



right optic disc somewhat nasally tilted with inverse vessel emergence On both sides pale ectasia nasally to the discs but of only -2 dioptres depth

Perimetry showed temporal visual field defects which disappeared with increasing target size but not by correction with minus glasses

Case 39

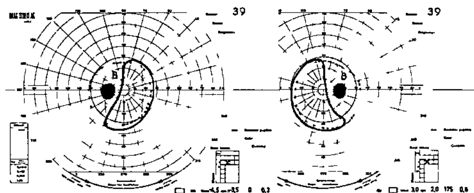
A 57 year old man (091206 J P E H) had always been myopic with astigmatism A deceased brother and the mother had also been myopic In 1955 the patient sought an eye doctor in connection with examination for headache As bitemporal hemianopia was found he was referred to the neurosurgical department of Rigshospitalet in København X ray examination of the cranium electroencephalography carotis angiography and pneumoencephalography showed normal conditions

Under later controls the visual field defect was found to be unchanged In connection with later investigation the patient was called in in 1968

Visual acuity R E 0 8 - 3 0 sph ⊃ - 2 0 cyl 175°
L E 0 25 - 4 5 sph ⊃ - 3 5 cyl 0°

Ophthalmoscopy In front of the optic discs and reaching a little beyond there was on both sides a prepapillar membrane most conspicuou on the left side The optic discs were slightly nasally tilted with inverse vessel emergence Nasal crescent on both sides and around this an ectasia of the fundus with pale bottom but without atrophies The bottom was seen most clearly with -10 dioptres

Perimetry showed bitemporal hemianopia for small targets but this disappeared on perimetry with larger targets and on correction with -8 dioptres

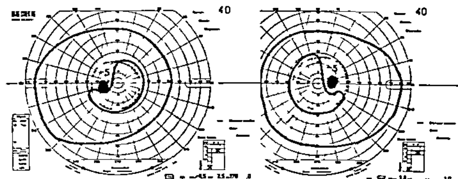


Case 40

A 69 year old man (990509 J H) father of patient no 23 was called in as a link in the investigation of the family Saw reportedly well in childhood without glasses Myopia was found on examination for military service and he got glasses when aged 21

Visual acuity R E 1 0 - 3 0 sph
L E 1 0 - 0 5 sph ⊃ - 2 5 cyl 170°

Ophthalmoscopy Small nasal crescent on both sides On the right side nasal ectasia of the fundus where the bottom was seen with -7 to -8 dioptres On the left side with -7 dioptres



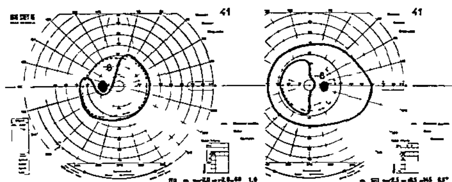
Case 41

A 45 year old woman (??0513 K H) sister of patient no 47 was seen in connection with family investigation Her vision had always been somewhat weak but she had not *had significant eye disorders*

Visual acuity R E 0 6 −9.5 sph ⊃−3.5 cyl 145°
L. E 1 00 − 2 0 sph ⊃− 2 0 cyl 60

Ophthalmoscopy The optic discs were vertically oval with inferior crescent and tilted somewhat nasally downwards Below and nasally to the optic discs there were pale ectasias of the fundus with degenerations The bottom was seen with −10 to −12 dioptres

Perimetry showed bitemporal hemianop a which disappeared on correction with −8 dioptres and with large targets



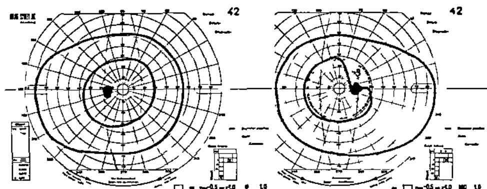
Case 42

A 3? year old man (350610 K E H) brother of patient no 23 was examined in connection with family investigation Thought he had always had rather weak sight but only 5 years before the examination had first obtained glasses after he found out his sight was better when he borrowed a pair of glasses one day

Visual acuity R E 1 0 – 0 5 sph ⊃ – 1 0 cyl 160°
L E 1 0 – 0.5 sph ⊃ – 1 0 cyl 0°

Ophthalmoscopy On both sides nasally below the optic discs there was a lesser ectasia of the fundus where the bottom was most sharply seen with –4 dioptres

Perimetry showed superior temporal visual field defect on the right eye which dis appeared on correction with –3 dioptres



Case 43

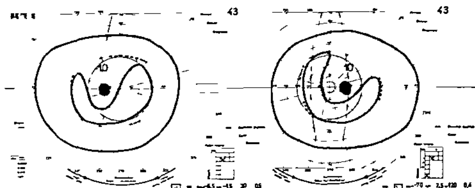
A 49 year old woman (230511 E M H) was interned in the eye department of Århus Kommunehospital because there was found a choroidal naevus

The patient had seen poorly from childhood sat in the front row at school but only got her first glasses when aged 18 The mother and 3 sisters used glasses for short sightedness while 5 brothers had good sight without glasses None had such strong glasses as the patient

Visual acuity R E 0 4 – 7 0 sph ⊃ – 2 5 cyl 120°
L E 0 5 – 6 5 sph ⊃ – 1 5 cyl 30°

Ophthalmoscopy The optic discs tilted a little downwards with nasal crescents The veins rather tortuous Below and nasally to the optic disc there was a pale ectasia region where the bottom was seen with –15 dioptres compared with the disc s –10 to –11 dioptres and the macular region s –7 to –8 dioptres

Perimetry showed bitemporal visual field defect for small objects which disappeared on correction with –10 dioptres



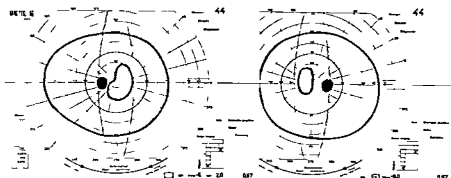
Case 44

A 51 year old woman (151018 E M H) was interned in 1967 in the ear department at Rigshospitalet in København for Meniere's disease On examination in the eye department I found

Visual acuity R E 0 67 – 8 0 sph
L E 0 67 – 6.5 sph ⊃ – 2 0 cyl 0

Ophthalmoscopy Inverse vessel emergence and ectasia of the fundus embracing the optic disc and the region lying nasally thereto The optic disc was 4 dioptres more myopic than the macula

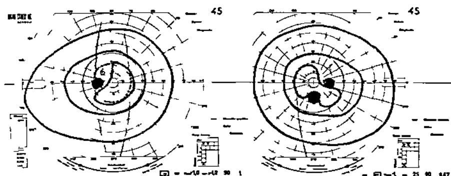
Perimetry With small targets there was bitemporal visual field defect



Case 45

A 38 year old man (81022 C O J) brother of patient no 47 was called in in connection with family investigation which was carried out at Rigshospitalet in København in 1967 His sight had not been completely good in childhood but he had managed without glasses until he was 20 Since then he had got stronger glasses twice but had not had other eye disorders

Visual acuity R E 0 67 – 1 0 sph ⊃ – 2 5 cyl 90°
L E 1 00 – 1 0 sph ⊃ – 1 0 cyl 90°



Ophthalmoscopy The right optic disc had a suggestion of inferior crescent the left was tilted downwards with inverse vessel emergence On both sides there was a pale ectasia of the fundus nasally to and embracing the optic disc the bottom of which was seen with -6 dioptres on the right side and -9 dioptres on the left side Above the optic disc on the right side there was an areolar choroideal sclerosis This was twice as big as the optic disc

Perimetry showed a bitemporal visual field defect for small targets On the left side this disappeared on correction with -6 dioptres On the right side there was a scotoma corresponding to the choroideal sclerosis

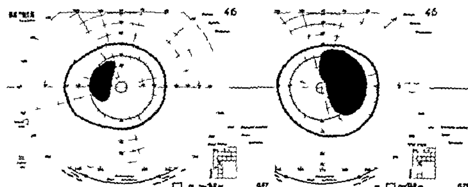
Case 46

A 59 year old woman (080715 C O J) was examined when she sought a practising eye doctor in København for control of glasses She had been near sighted since childhood but had otherwise no eye disorders

Visual acuity R E 0 95 - 13 0 sph
L E 0 67 - 8 0 sph

Ophthalmoscopy Both optic discs tilted nasally downward with inverse vessel emergence and inferior crescent Obvious ectasia nasally to and partly embracing the optic disc region Nasally downwards from the right optic disc there were typical myopic degenerations

Perimetry showed bitemporal visual field defects which only diminished in part on increasing the target size and correcting with minus glasses



Case 47

A 3? year old woman (341229 B B J) was interned in 1966 in the eye department at Rigshospitalet in København for detached retina in the right eye The patient s sister and brother cases 41 and 45 are included in this material (pedigree no 1) She had always had poorer sight in the right eye than in the left The detachment had occurred 7 weeks prior to the internment

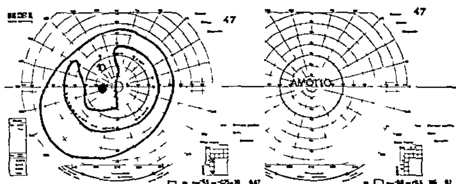
Visual acuity R E (after detachment operation) 0 1 - 9 0 sph
L E 0 67 - 6 5 sph ⊂ - 0 75 cyl 10°

Slightly prominent eyes

Ophthalmoscopy On internment there was found on the right side a big widespread detachment with a little peripheral hole at 11 o clock

After the operation there was seen an inferior crescent inverse vessel emergence and nasally downward tilted optic discs on both sides Nasally downward from the optic discs there were ectasia of the fundus the bottom of which was seen with −20 dioptres

Perimetry on the left side showed temporal visual field defect for small targets which disappeared on correction with −10 dioptres



Case 48

A 60 year old man (0/0330 C A J) was interned in 1967 in Kommunehospitalet in København During his stay he developed conjunctivitis and for this he was referred to the eye clinic

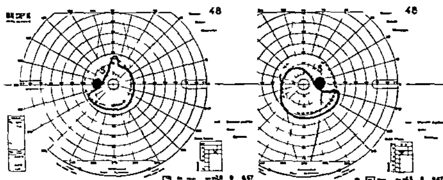
Visual acuity R E. 0 67 + 1.5 cyl 0
L E 0 67 + 2 0 cyl 0

Appearance mobility Normal

Ophthalmoscopy The optic discs slightly nasally tilted with inverse vessel emergence and ectasia of the fundus nasally to the optic discs where the bottom was seen with −5 dioptres No crescent Medullated nerve fibres on the right side

Perimetry Did not co operate well Relative defects corresponding to the ectasia of the fundus which disappeared with −5 dioptres correction

Intraocular pressure both eyes 12 mm appl



Case 49

A 22 year old man (450128 H G J) was during military service referred to Rigshospitalet in København for control of glasses

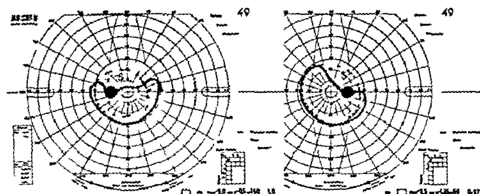
He had been short sighted since childhood and got glasses when he began school He had later got gradually stronger glasses

Visual acuity R E 0 67 – 5 5 sph ⊂ – 1 25 cyl 50°
L E 1 0 – 3 0 sph ⊂ – 0 50 cyl 150°

Appearance position mobility normal

Ophthalmoscopy The optic discs tilted slightly nasally with inverse vessel emergence and nasal crescent margin Nasally below the optic disc was a pale ectasia of the fundus where the bottom could be seen with –8 to –9 dioptres

Perimetry showed superior bitemporal defects with small targets These disappeared on correction with –5 dioptres

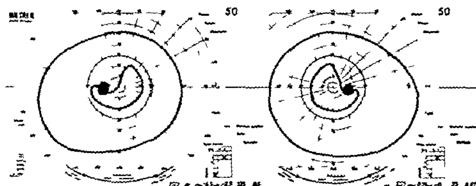


Case 50

A 55 year old man (11031 G K) had in the course of one year been treated 3 times *for detached retina in the left eye by photocoagulation and once with siliconcerclage*

He was otherwise generally well No eye disorders in the family The patient had used glasses since childhood

Visual acuity R E 0 67 – 2 75 sph ⊂ – 0 5 cyl 25°
L E 0.50 – 4 75 sph ⊂ – 2 0 cyl 125°



Ophthalmoscopy Retina attached everywhere on both sides The optic discs tilted nasally with a whitish lower nasal crescent Around that was a pale ectasia of the fundus where the bottom was seen with -8 dioptres on the right side and -10 dioptres on the left side

Inverse vessel emergence on both sides

Perimetry Bitemporal visual field defects which disappeared with larger targets

Case 51

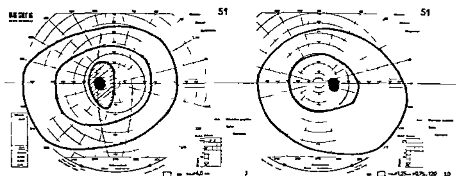
A 35 year old woman (310978 E.J.K.) sought a practising eye doctor in København with a view to control of glasses The father used glasses otherwise there were no eye disorders in the family The patient had been operated for convergent squint in the left eye at the age of 5 Had always seen poorly with the left eye and used reading glasses since childhood

Visual acuity R E 1 0 + 2 0 sph ⊂ - 0 75 cyl 30°
L E 0 1 + 4 0 sph

Parallel eye position uncertain central fixation in the left eye.

Ophthalmoscopy Normal conditions on the right side The left optic disc was tilted nasally with inverse vessel emergence The region around the optic disc was rather pale with some ectasia and was seen with -2 dioptres as against +4 in the centre

Perimetry showed normal conditions on the right side On the left side there was a relative temporal scotoma corresponding to the ectasia One can not completely exclude the possibility that suppresion after squinting was a contributary cause in this case



Case 52

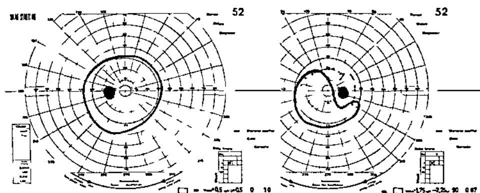
A 38 year old woman (280421 K.K.L.) sought the eye doctor in København for eye strain The patient had used glasses since chool age and had never had quite good sight The father had astigmatism

Visual acuity R E. 0 67 - 1 75 sph ⊂ - 2.25 cyl 90°
L E 1 00 + 1 00 sph ⊂ - 0.50 cyl 90°

Moderately asymmetrical features The right temporal region somewhat more prominent than the left No exophthalmos Position and mobility normal

Ophthalmoscopy The right optic disc pale with nasal crescent Obvious nasally tilted optic disc inverse vessel emergence and pale ectasia of the fundus nasally to the disc The bottom was seen with -7 dioptres The left fundus normal

Perimetry Scotoma temporally on the right side which disappeared on correction with -7 dioptres



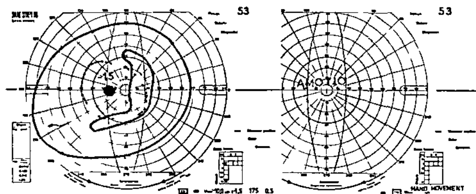
Case 53

A 28 year old woman (350924 E E L) had been shortsighted since childhood The refraction had in the course of the last 12 years been increased from -6 to -10 dioptres in the left eye Had been previously treated with diathermy for detached retina in the left eye with good result On internment in Rigshospitalet in København in 1966 for detached retina in the right eye the patient was in the 8th month of pregnancy At this time there was a large detachment with visual field only preserved in the lower temporal quadrant In the upper temporal quadrant of the retina there were 5 holes one of which was very big

Visual acuity L E 0 5 – 10 0 sph ⊃ – 1 5 cyl 1/5°

Ophthalmoscopy L E The optic disc had nasal crescent margin and inverse vessels Considerable pale ectasia of the fundus nasally to the optic disc where the bottom was seen with -20 dioptres

Perimetry showed temporal visual field defect on the left side which disappeared on correction with -15 dioptres



Case 54

A 43 year old man (?40813 P A L) had always seen poorly with the right eye A brother had reportedly the same disorder

The patient had been previously operated for pterygium in the right eye He was now interned in the medical department for heart disease and was referred to Rigs hospitalet in København for examination for exophthalmus Several doctors had pre viously remarked that he had somewhat prominent eyes and he himself did not think this had increased

On examination in 1968 there was found

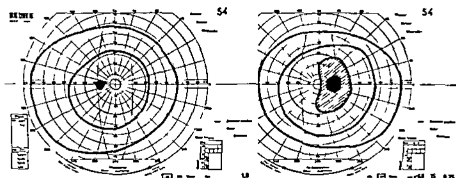
Visual acuity R E 0 33 + 1 0 sph. ⊂ − 5 0 cyl 10°
L E 1 00 emmetropia

Exophthalmometry 19–18/101 mm

Ophthalmoscopy The right optic disc was pale nasally tilted with nasal crescent and inverse vessel emergence

Outside this there was a nasal ectasia of the fundus in which the bottom was most sharply seen with −20 The vessels were stretched nasally and bent temporally On the left side the optic disc was a little reddish with slightly nasally tilted vessel emergence otherwise normal condition.

Perimetry showed relative scotoma temporally on the right side



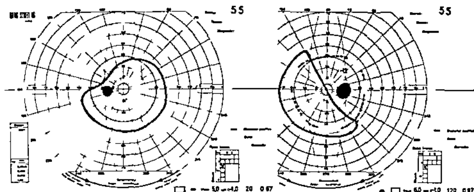
Case 55

A 19 year old woman (450209 A G M) was examined in connection with the family investigation being the daughter of patient no 56 Got glasses in early schoolage and later the strength had gradually been increased No other eye disorders

Visual acuity R E 0 67 − 6 0 sph. ⊂ − 1 0 cyl 1?0°
L E 0 67 − 5 0 sph ⊂ − 1 0 cyl ?0

Ophthalmoscopy On the right side there was inferior crescent on the optic disc slightly inverse vessel emergence and nasally downwards from the optic disc a typ cal ectasia of the fundus with myopic degeneration in the bottom which was seen with −15 dioptres On the left side the optic disc was normal and there was only a 2 dioptres deep ectasia of the fundus nasally

Perimetry showed refractionally determined scotoma temporally on the right side which disappeared on correction with −1? dioptres



Case 56

A 46 year old woman (201224 L A M) had been shortsighted since childhood 3 of her 4 children used glasses one of these being patient no 55 A son had also ectasia of the fundus and visual field defect but since he was not examined in the Goldmann perimeter he is not considered in this material The patient had not had other eye disorders

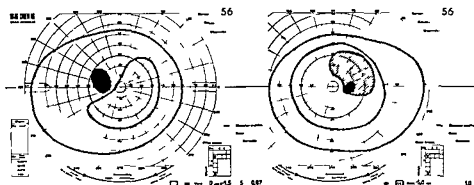
Visual acuity R E 1 00 – 5 0 sph
L E 0 6/ – 7 0 sph ⊂ – 1 5 cyl 15°

10 degrees alternate divergent strabismus without glasses only 5 degrees with glasses

Ophthalmoscopy The optic discs were tilted nasally downwards with a broad crescent margin and inverse vessel emergence Pronounced ectasia of the neighbouring region and especially nasally to the optic disc where the bottom was seen with –15 dioptres on the right side and –20 dioptres on the left

On the left side there were myopic atrophies corresponding to the bottom of the ectasia

Perimetry showed superior bitemporal visual field defects for small targets The defects diminished with minus correction and increasing target size



Case 57

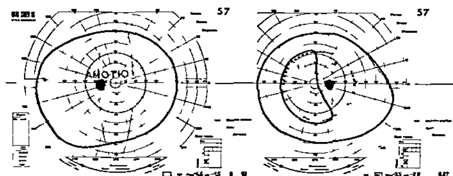
A 58 year old woman (080219 E M) was treated for detached retina with tear in the left eye in 1960 The retina was re attached The patient was seen after she had been

treated in 1966 at Rigshospitalet København for hole with incipient retinal detachment in the right eye Photocoagulation was carried out with good result

Visual acuity R E 0 67 – 3.5 sph. ⊃ – 2 0 cyl 0°
L. E. 0 10 – 4.5 sph ⊃ – 1.5 cyl. 0

Ophthalmoscopy The optic discs tilted nasally downwards with inferior crescent The vessels stretched downwards but bending over the upper margin Below and nasally to the optic discs there was an ectasia of the fundus where the bottom was most sharply seen with –12 dioptres on the right side while on the left side there were only 2 dioptres ectasia

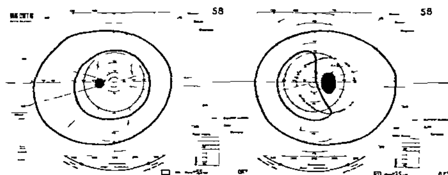
Perimetry On the right side there was a temporal visual field defect for small objects which disappeared on correction with –7 dioptres On the left side the conditions were difficult to judge because of the poor central vision in the connection with the earlier detachment



Case 58

A 68 year old man (990812 R E M) was referred to Kommunehospitalet, København, in connection with diabetes mellitus which he had for 10 years There were not found any diabetic changes in the fundus

Visual acuity R E. 0 6 + 3.5 sph
L. E 0 67 + 5.5 sph



Ophthalmoscopy The optic disc on the right side was tilted nasally downwards with inverse vessel emergence and a wide inferior nasal crescent margin Around this there was an obvious pale ectasia of the fundus where the bottom was seen most sharply with -8 dioptres whereas the macula was seen with +3 On the left side conditions were normal

Perimetry showed temporal visual field defect for small targets on the right side which disappeared on correction with -6 dioptres

Case 59

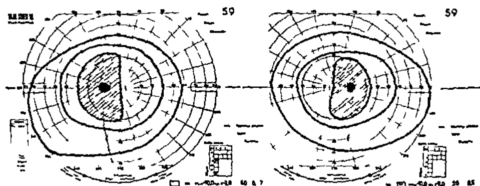
A 59 year old woman (080470 A L M) had seen poorly since childhood She is the mother of patient no 32 So far as she could remember she had always had prominent eyes Exophthalmus had been remarked upon at an examination in the eye department at Rigshospitalet København in 1950

Upon examination in 1967 there was found

Visual acuity R E 0 50 - 10 0 sph ⊃ - 2 0 cyl 20°
L E 0 67 - 10 0 sph ⊃ - 2 0 cyl 160°

Ophthalmoscopy The optic discs were pale with nasal crescent and inverse vessel emergence There was ectasia of the fundus nasally to the optic discs where the bottom was seen with -15 dioptres as compared to -10 dioptres in the centre

Perimetry showed bitemporal visual field defects corresponding to the ectasias of the fundus which disappeared with increasing target size



Case 60

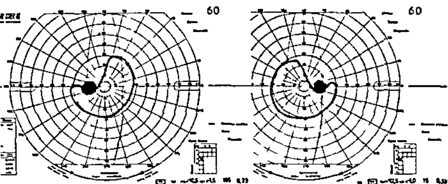
A 36 year old man (300507 F S H) had had poor sight since childhood and was now referred to Rigshospitalet København for periodical headache and failing sight

Visual acuity R E 0 33 - 12 5 sph ⊃ - 1 0 cyl 15°
L E 0 33 - 10 5 sph ⊃ - 1 5 cyl 165°

Cornea chamber iris and lens normal

Ophthalmoscopy The optic discs were pale with inferior crescent and nasally tilted vessel emergence The retinal region below and nasally to the optic discs was pale but with only a few dioptres ectasia of the fundus

Perimetry showed bitemporal hemianopia which almost disappeared on correction of the myopia



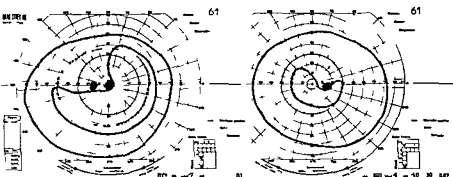
ıse 61

30 year old woman (360S04 E L P) got glasses for myopia when 12 years old and .d changed them several times since In the later years she had seen poorly with the ft eye and was not completely sure that she had ever seen well with that eye In 1966 e was referred to Rigshospitalet København because during a control of her glasses e eye doctor had found changes in the centre of the left eye These were judged to : myopic degenerations

ısual acuity R E 0 67 – 5 5 sph ⊂ – 1 0 cyl 30
L E 0 10 – 7 0 sph

phthalmoscopy On the right side the optic disc was pale and there was a 3–4 dioptres ɛep ectasia of the fundus nasally to the disc On the left side there was inverse vessel nergence and a large pale ectasia of the fundus with degenerations nasally to the ptic disc There was also myopic degeneration in the macular region

Perimetry Superior bitemporal relative visual field defects together with central otoma on the left side



:ase 62

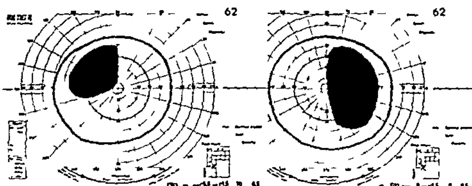
\ 51 year old man (1606?9 E D P) had seen poorly in his schooldays but on economic ;rounds had not had glasses before he was grown up Subsequently the myopia had ncreased somewhat.

In connection with internment in Kommunehospitalet København in 1967 he was examined in the eye clinic

Visual acuity R E 0.5 − 7 0 sph ⊃ − 1 5 cyl 10°
L E 0.5 − 5 0 sph ⊃ − 1.5 cyl 10°

Ophthalmoscopy The optic discs tilted nasally downwards with pronounced nasally directed vessel emergence Nasally and below there was a crescent which merged into myopic degeneration Nasally to the optic discs there was an ectasia of the fundus where the bottom was seen with −15 dioptres

Perimetry showed bitemporal scotomata corresponding to the ectasia of the fundus



Case 63

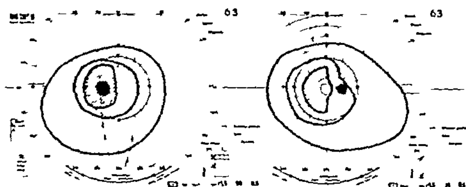
A 60 year old woman (050707 P K R) was interned in the medical department at Århus Kommunehospital for diabetes mellitus and in connection with that was referred to the eye clinic

No eye changes of diabetic origin were found

Visual acuity R E 0 5 − 1 5 cyl 135
L E 0 5 − 1 5 cyl 90°

Ophthalmoscopy The optic discs were slightly tilted nasally downwards with nasally directed vessel emergence and inferior nasal crescent margin Nasally to the optic disc there was a pale ectasia of the fundus only a few dioptres deep

Perimetry Bitemporal visual field defects which diminished with increasing target size



Case 64

A 33 year old woman (3>0403 I S) had been examined by an eye doctor several years earlier in connection with headache The discovery of bitemporal hemianopia led to internment in the neurological department of Rigshospitalet København

X ray examination of the cranium electroencephalography spinal fluid examination carotid angiography and pneumoencephalography showed normal condition. Later the patient was controlled several times at Rigshospitalet, København Tagensvej The visual field defects remained unchanged

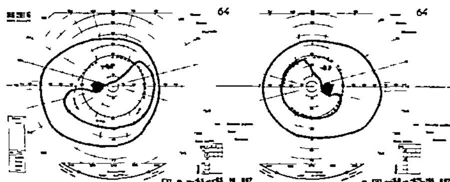
On examination in 1968 was found

Visual acuity R E 0 67 – 5 0 sph. ⊃ – 0 75 cyl 150
L. E 0 67 – 6.5 sph ⊃ – 0.50 cyl 10

Slightly conspicuous eyes Exophthalmometry 16–16/97 mm

Ophthalmoscopy Downward tilted optic discs with little inferior crescent. Pale ectasia of the fundus nasally downward from the optic discs where the bottom was seen with –12 dioptres

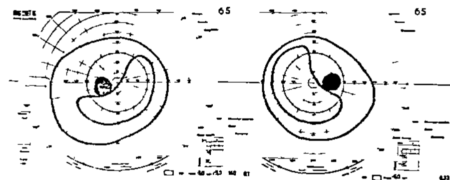
Perimetry Superior bitemporal visual field defects which disappeared upon correction with –9 dioptres and with increasing target size



Case 65

A 65 year old woman (0.0712 G S) had always had poor sight but had never had glasses or sought the eye doctor Appeared moderately mentally retarded Now sought a practising eye doctor regarding glasses

Visual acuity R E 0 33 – 6 0 sph
L. E 0 10 – 3 0 sph ⊃ – 3 0 cyl 140



Incipient cortical lens opacities on both sides but insufficient to explain the reduction in visual acuity

Ophthalmoscopy The optic discs tilted downwards with inverse vessel emergence and inferior crescent Nasally downwards from the optic discs were seen pale ectasia of the fundus where the bottom was seen with –12 dioptres

Perimetry Somewhat inexact reporting because of poor cooperation Definite superior bitemporal visual field defects with small targets

Case 66

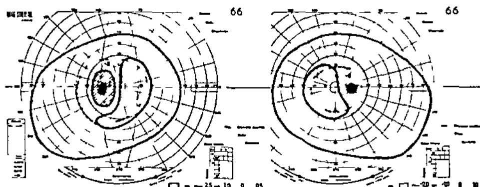
A 25 year old man (430526 N O) had as a child a squint which disappeared without treatment He got glasses when aged 7–8 As a soldier he reported poor night vision He was examined in th eye department at Rigshospitalet København where electro retinography and night vision adaptation showed normal condition The discovery of bitemporal hemianopia resulted in his being excused military service At a control examination the findings were

Visual acuity R E 1 0 – 2 0 sph ⊃ – 1 0 cyl 0°
L E 0 5 – 5 5 sph ⊃ – 1 0 cyl 0°

Appearance position and mobility normal

Ophthalmoscopy The optic discs tilted nasally downwards with inverse vessel emergence and small crescent especially on the right side Nasally downwards from the discs was seen a clear ectasia of the fundus where the bottom of the right side could be seen with –8 dioptres and on the left side with –15 dioptres

Perimetry Bitemporal visual field defects which disappeared on correction with –8 dioptres



SUMMARY

The object of this work has been to describe an eye anomaly consisting of a series of individual characteristics As a name for the disorder the nasal fundus ectasia has been selected Special attention has been paid to the bitemporal visual field defects which can easily lead to a suspicion of tumour in the region of the optic chiasm

Chapter 1

The individual findings in the nasal fundus ectasia are separately reviewed The inferior nasal crescent dysversion of the optic disc inverse vessel emergence and the ectasia of the fundus are described commencing with earlier literature Moderately impaired visual acuity myopia and astigmatism belong to the symptoms complex

The etiology is discussed under the individual sections but also in a section of its own in which are reviewed the whole anomaly s etiology and histology based on the available literature

The possibility of connection with *other ophthalmological disorders* or *general diseases* is discussed

Under *genetics* the references in literature to cases of family occurrence are cited There is not enough evidence from which to draw any conclusions about the mode of inheritance

Chapter 2

The selection of patients and the methods of investigation are reviewed

The patients are mostly found in hospital out patient clinics by routine perimetry in connection with other diseases 8 cases emerged from examination of the patients nearest relatives By going through a patient material with bitemporal hemianopia of unknown cause in a neuro surgical department a further 8 cases were found

The *refraction* was measured firstly by subjective methods but in many cases also by refractometry and retinoscopy The corneal astigmatism was in all cases measured with Schiotz – Javal ophthalmometer

Ophthalmoscopy was carried out under mydriasis Search was specially direct

ed towards *crescent dysversion inverse vessel emergence ectasia of the fundus* and *degenerative lesions* and in the majority of cases the fundus was photo graphed

Perimetry was in the first instance performed with small targets on a Bjerrum - screen but for the final examination a Goldmann perimeter was used

The fundus ectasia s depth was measured by ophthalmoscopy but in a few cases also by retinoscopy refractometry and ultra sonic examination

Chapter 3

Based on the material of 115 eyes in 66 patients with visual field defects together with fundus ectasia it appears that the incidence of the anomaly is about the same for men and women About as many patients were referred in connection with general diseases as with eye disorders

Scarcely 1/4 of the eyes had visual acuity 1 0 – the majority lying within the range 0 33 to 1 0 90 % of the eyes with this anomaly were myopic and 70 % had astigmatism more than 1 dioptre

Ophthalmoscopically over half of the patients showed a distinct inferior nasal crescent Dysversion was present in 65 % and inverse vessel emergence in 80 % of the eyes

The fundus ectasia was in 102 of 115 eyes deeper than 2 dioptres In most cases the depth lay between 4 and 8 but in some reached to 15 dioptres In 90 % of the cases the fundus was pale in the region of the ectasia and in 14 eyes principally of elderly patients there were found degenerative lesions

Perimetry showed bitemporal relative visual field defects which in Gold mann s perimeter were largely revealed with target 1 = 1/4 mm In most cases the visual field defects were reduced or disappeared on correction of the eye with glasses corresponding to the floor of the ectasia

X ray examination of the orbit and *electroretinography* applied in a few cases showed normal conditions

The *fundus ectasia s* depth was judged by ophthalmoscopy and in some cases also by retinoscopy refractometry and ultrasonic examination By far the easiest and most practical method was point ophthalmoscopy but all methods gave fairly consistent results

On the 66 patients in the material 9 had undergone extensive examination in the neuro surgical department because bitemporal hemianopia had been found Three of these were submitted to exploratory craniotomy for suspected pituitary tumour

Of *other eye disorders* there were found 6 cases of slight exophthalmos 4 cases of detached retina and 3 cases of squint These are discussed

No grounds were found for presuming that general diseases have any con nection with the anomaly

Chapter 4

The conclusion contains an appreciation of what can be said about the nasal fundus ectasia on the basis of the literature collated with the material Emphasis is given to the etiological genetical clincal and neuroophthalmological aspects

Chapter 5

The pedigrees of 8 families are drawn up

Chapter 6

The case histories of the 66 patients and the examination are reviewed together with the visual field diagram

Andersen O C Weitere Erfahrungen mit der quantitativen Perimetrie *Albrecht v Graefes Arch Ophthal* 1944 *147* 227–249 (19 24)

Badke G Koni in orthotypischer und heterotypischer Richtung Der Augenartzt Vol 4 Leipzig Thieme 1961 128–159 (19 23 27)

Ballentyne A J & Michaelson I C Textbook of the Fundus of the Eye Edinburgh Livingstone 1970 p 471 (14)

Bard L A Tilted disc with inferior conus a report of 12 cases
Ref 26th Meeting of the Wilmer Residents Association
Arch Ophthal (Chicago) 1967 *78* 688 (23 24)

Bedell A J Retinal Folds *Amer J Ophthal* 1966 *61* 1000–1002 (17 27)

Beeler A Der hetrotypische Conus inbesondere der Conus nach unten und die Aus buchtung des angrenzendes Augenhintergrundes *Albrecht v Graefes Arch Ophthal* 1929 *122* 342–258 (12 14 15 16 17 21 22 23 24 27 28 30 42)

Behse F Über den anatomischen Bau der Conus und der Aderhautveranderungen im Myopischen Auge *Albrecht v Graefes Arch Ophthal* 1908 *67* 379–438 (21 27)

Berry H Bitemporal Depression of the Visual Fields due to an Ocular Cause *Brit J Ophthal* 1963 *47* 441–444 (14 22 23)

Betsch A Über die menschliche Refraktionskurve *Klin Mbl Augenheilk* 1929 *82* 365–379 (41)

Birge H L Myopia Caused by Prematurity *Trans Amer Ophthal Soc* 1955 *53* 219–228 (30)

Black R K Jay B & Mac Faul P The Concept of Degenerative Myopia *Proc of the Royal Soc of Med* 1965 *58* 109–112 (28)

Blatt N Gesichtfeldveranderungen bei hochgradigen Myopen *Klin Mbl Augenheilk* 1964 *145* 680–?12 (24)

Bonamour G & Leopold P Les Croissants et les Dysversions de la Papille *Conferences Lyonnaises d'Ophtal* 1960 N° 50 Numero Special (12 14 15 16 19 23 26 27)

Bonamour G Maculopathies acquises et Malformations Papillaires *Bull Soc Ophtal Franc* 1964 *4* 417–420 (26)

Bonamour G Bregeat P Bonnet M & Juge P La Papille Optique Paris Masson 1968 p 83–88 and p 146–164 (16 23 30)

Bonamour G Amblyopie Fonctionelle et Malformations Papillaires a Minima *Bull Soc Belge Ophthal* 1969 *151* 338–341 (22)

Brændstrup P Vitreous Haemorrhage in the Newborn *Acta Ophthal* (København) 1969 *47* 502–513 (17 2[illegible])

Bucklers M Ueber doppelseitige nasale Fundusektasie Sitzungberichte Wurttenbergische augenarzliche Vereinigung *Klin Mbl Augenheilk* 1936 *96* 119 (19 22 23)

Bynke H Personal Communication 1967 (24)

Caccamise W C Situs inversus of the optic Disc *Amer J Ophthal* 1954 38 854–856 (19 22 23 24)
Cavara Studio Clinico – stastico sull – astigmatismo inverso *Boll Oculist* 192? I 301–334 (?4)
Chadwick A J Inversion of the Disc and temporal Field loss in chronic simple glaucoma *Brit J Ophthal* 1968 52 932–933 (?4 ?6)
Chandler P A & Grant W M Lectures of Glaucoma Philadelphia *Lea & Febiger* 1965 p 28 (26)
Collier M Frequence de vaisseaux cilio rétiniens leur assosiation avec d autres anomalies du fond de l oeil *Bull Soc Opht de France* 195 9 598–601 (16 17)
Didier Laurent I Malformations papillaires et maculapathies These Medicine Lyon 1966 (?6)
Duke Elder W S System of Ophthalmology Vol III part ? London Kimpton 1964 p 288 and 674–678 (14 16 23 27)
Duke Elder W S System of Ophthalmology Vol V London Kimpton 1970 p 280 (?4)
Edmund C On Congenital Colobomatous Groove Formations in the Optic Disc *Acta Ophthal (Kobenhavn)* 1930 8 56–63 (14 ?6)
Elschnig A Das Colobom am Sehnerveneintritte und der Conus nach unten *Albrecht v Graefes Arch Ophthal* 1900 51 391–4?9 (17 ?1 2 28)
Elschnig A Ueber Conus nach unten und Colobom am Sehnerveneintritte *Bericht uber die ?8 versamlung der Ophthal Gesellschaft 1900–1901* p 214–219 (?7)
Elschnig A Weitere Mitteilung uber das Colobom am Sehnerveneintritte und den Conus nach unten *Albrecht v Graefes Arch Ophthal* 1903 56 49–65 (21 27)
Enokson P Bitemporala Synsfaltdefekter vid bakre staphylom *Nord Med* 1960 63 830–831 (14 19 22 23 24 25)
Enokson P Perimetry in Neuro Ophthalmological Diagnosis *Acta Ophthal* (Kobenhavn) Suppl 8? 1965 p 11 14 (14 2?)
Ernyei S Distortion of the Optic Nerve Papillae *Amer J Ophthal* 1964 57 1054–1055 (14 24 27 30)
Ferree C E & Rand G Interpretation of Refractive Conditions in the Periferal Field of Vision *Arch Ophthal (Chicago)* 1933 9 925–938 (19)
Fledelius H Ultrasound (A Mode) in a case of Nasal Posterior Scleral Ectasy *Acta Ophthal* (København) 1970 48 50?–507 (?1 34 48)
Fletcher M C & Branden S Myopia of Prematurity *Amer J Ophthal* 1955 40 474–481 (30)
Francois J Goes F & Yobbagyi P Etude biometrique d une ectasie sclerale peri papillaire congenitale (Staphylome posterieur vrai) *Ophthalmologica* 1967 154 446–460 (?1)
Frankenhauser F & Enoch J M The Effects of blur upon Perimetric Threshold *Arch Ophthal* (Chicago) 1962 68 240–251 (21 25)
Fuchs A Myopia Inversa *Arch Ophthal* (Chicago) 1947 37 7??–739 (14 19 23 26 27 28)
Fuchs E Beitrage zu den angeboren Anomalien des Sehnerven *Albrecht v Graefes Arch Ophthal* 188? 28 139–169 (14 15 17 21 22 23 24 26 27 30)
Fuchs E Über den anatomischen Befund einiger angeborner Anomalien der Netzhaut und des Sehnerven II Sichel nach unten an der Papille *Albrecht v Graefes Arch Ophthal* 1917 93 ?0–28 (14 21 24 27)
Fuchs E Über Heterochromie nebst Bemerkungen uber angeborne Anomalien *Albrecht v Graefes Arch Ophthal* 1917 93 381–398 (19)

Gardiner P A & James G Association between Maternal Disease during Pregnancy and Myopia in Child *Brit J Ophthal* 1960 *44* 172–178 (30)

Garzo C A & Poggi J M E Pseudo Hemianopsia Bitemporal *Arch Ophthal* (B Aires) 1963 38 292–293 (24)

Goldschmidt E On the Etiology of Myopia *Acta Ophthal* (Kobenhavn) Suppl *98* 1968 163–164 (30)

Goldmann H Grundlagen exakter Perimetrie *Ophthalmologica* 1945 *109* 57–70 (24)

Graham M V Visual Field Defects Associated with Anomalies of the Optic Discs *Proc Roy Soc Med* 1972 *65* 523 (14 24)

Graham M V & Wakefield G J Bitemporal Visual Field Defects Associated with Anomalies of the Optic Discs *Brit J Ophthal* 1973 *57* 307–314 (17 19 24 26)

Gruenwald P Studies of Development Developmental Pathology *Amer J Anat* 1944 *74* 217–258 (28)

Grondahl J Heterotopia Maculae *Acta Ophthal* (Kobenhavn) 1963 *41* 259–261 (26)

Hiatt R L Costenbader F D & Albert D G Clinical Evaluation of Congenital Myopia *Arch Ophthal* (Chicago) 1965 *74* 31–35 (28 30)

Hoffmann H Ueber eine seltene Strangbildung im Augenhintergrund *Klin Mbl Augenheilk* 1926 *77* 370–379 (15 26 27 30)

Hoyt W F Personal Communication 1971 (21 25 26)

Jensen O A Malignant melanomas of the Uvea in Denmark Kobenhavn Munk gaard 1963 p 65 (37)

Kestenbaum A Clinical Methods of Neuro Ophthalmologic Examination New York *Grune & Stratton* 1961 p 113 (26)

Kommerell G Binasale Refraktionsscotome *Klin Mbl Augenheilk* 1969 *154* 85–88 (21 23)

Kral K & Svarc D Contractile peripapillary Staphyloma *Amer J Ophthal* 1971 *71* 1090–1092 (17)

Kronfeld P C & Devney C The Frequency of Astigmatism *Arch Ophthal* (Chicago) 1931 *4* 873–884 (24 47)

Kruse W & Utermann D Beitrag zur Erkennung refraktionsbedingter Skotome *Klin Mbl Augenheilk* 1963 *143* 247–259 (14 19 21 22 23 24 27)

Lang B T The Position of the Axis in Astigmatism and the Amount of the Astigmatic Error from an Analysis of four thousand Prescriptions *Brit J Ophthal* 1920 *4* 126–128 (24)

Lauber H Klinische und anatomische Untersuchungen uber lochformige partielle Kolobome des Sehnerven *Zeitschrift f Augenheilk* 1909 *21* 494–504 (14 26)

Leopold P Les Croissants et les Dysversions de la Papille *Thèse Medecine* Lyon 1960 (12 1 22 23 24 25 30)

Lisch K Über hintere Scleralectasie *Bericht Deutsche Ophthal Ges* 1949 *55* 407–404 (19 23)

Lorentzen S F Drusen of the Optic Disc Kobenhavn Munksgaard 1966 p 36–37 (37)

Luhl C Ueber die Haufigkeit des Astigmatismus und seiner Beziehungen zur Sehscharfe Thesis Marburg *Koster & Schnell* 1909 (24)

Lohlein W Ueber nasale Fundusectasie bei Conus superior et inferior *Klin Mbl Augenheilk* 1934 93 439–446 (14 19 24 26)

Mann I Developmental Abnormalities of the Eye London *William Clowes & Sons* 1957 p 113 (15 28 30)

Manor R S Temporal Field Defects due to Nasal Tilting of Discs *Ophthalmologica* 1974 *168* 269–281 (17 19 22 23 24 26)

Michel J Contribution a l etude des ectopies de la Macula *These Medicine* Lyon 1959 (17 26)
Mollenbach C J Medfodte Defekter i Ojets indre Hinder Kobenhavn Nyt Nordisk Forlag 1947 p 21 (27)
Odland M Bitemporal Defects of the Visual Fields due to Anomalies of the Optic Discs *Acta Neurol Scand* 1967 *43* 630–639 (22 23 24)
Paulsen O Über die Entstehung des Staphyloma posticum Choroideae *Albrecht v Graefes Arch Ophthal* 1882 *28* 225–244 (14 24)
Riise D Visual Field Defects in Optic Disc Malformation with Ectasia of the Fundus *Acta Ophthal* (Kobenhavn) 1966 *44* 906–918 (14 19 22 23 24 25)
Riise D Neuro opthalmological patients with bitemporal hemianopsia *Acta Ophthal* (Kobenhavn) 1970 *48* 685–690 (31)
Rucker C W Bitemporal Defects in the Visual Fields Resulting from Developmental Anomalies of the Optic Discs *Arch Ophthal* (Chicago) 1946 *35* 546–555 (14 17 22 23 24 25)
Ronne H Konusbildung und exzessive Myopie nasal zur Papille *Klin Mbl Augenheilk* 1916 *57* 512–517 (14 17 21 22 23 24)
Ronne H Die Erkrankungen der Papille Kurzes Handbuch der Ophthalmologi Vol V Berlin Springer 1930 p 615–619 (27)
Salzmann M Zur Anatomie der angeboren Sichel nach innen unten *Albrecht v Graefes Arch Ophthal* 1893 *39* 131–150 (27)
Salzmann M Konus oder Halo *Albrecht v Graefes Arch Ophthal* 1941 *143* 547–593 (21 27)
Scheerer R Zur entwiklungsgeschichtlichen Auffassung der Brechzustande des Auges *Bericht Deutsche Ophthal Ges* 1928 *47* 118–126 (41)
Scheerer R Über atypische Kolombome und ihre Beziehungen zur Myopie Bericht Deutsche Ophthal Ges 1930 *Klin Mbl Augenheilk* 1930 *85* 128 (27)
Schmidt T Perimetrie relativer Scotome *Ophthalmologica* 1955 *129* 303–315 (14 19 24 25)
Schnabel J Zur Lehre von den Ursachen der Kurzsichtigkeit *Albrecht v Graefes Arch Ophthal* 1874 *20 part 2* 1–70 (27)
Seefelder R Über die Entwicklung des Sehnerveneintrittes beim Menschen zugleich ein Beitrag zur Frage der Faltenbildungen in der embryonalen Netzhaut *Albrecht v Graefes Arch Ophthal* 1921 *106* 114–126 (27)
Sorsby A Modern Ophthalmology Vol 3 London Butterworths 1964 p 266 (27)
Stiles W & Crawford B The Luminous Efficiency of Rays entering the Pupil at Different Points *Proc Roy Soc B* (London) 1933 *112* 428–450 (23)
Symens H Anatomischer Befund bei einem myopischen nasalen Conus *Archiv fur Augenheilk* 1902 *44* 336–338 (27)
Szily A von Der Conus nach Unten *Zeitblatt prakt Augenheilk* 1883 7 358–362 (14 17 19 21 22 23)
Szily A von Über den Conus in heterotypischer Richtung Albrecht v Graefes Arch Ophthal 1922 *110* 183–291 (12 14 17 19 21 22 23 27 42)
Szily A von Die Morphographie und Phanogenetik der Papilla nervi opticee *Klin Mbl Augenheilk* 1955 *126* 641–669 (14 21)
Sorensen S K L astigmatisme du Christallin determiné comme la différence entre L astigmatisme Corneen et L astigmatism total illustre par L examen de ses variations d apres L age *Acta Ophthal* (Kobenhavn) 1944 *22* 341–385 (24)
Tertsch R Der Conus in atypischer Richtung *Albrecht v Graefes Arch Ophthal* 1913 *84* 530–553 (21 27 28)

Trier H G & Bohm H V B Bild bei inverser Papille mit hintere Staphylom Diagnostica Ultrasonica in Ophthalmologia 2 Symposium internationale de diagnostica ultrasonica in Ophthalmologia Brno J Vanysek 1968 p 263–266 (21 24 25)

Veirs E P Inversio Papillae with Altitudinal Fields *Amer J Ophthal* 1951 *34* 1596–1597 (17 26)

Vogt A Weitere Augenstudien an einigen Zwillingen hohere Alters uber die Vererbung der Altersmerkmale *Klin Mbl Augenheilk* 1938 *100* 497–544 (30)

Vossius A Beitrag zur Lehre von den angebornen Conis *Klin Mbl Augenheilk* 1885 *23* 137–157 (12 14 15 21 22 23 24 30)

Waardenburg P J Genetics and Ophthalmology Assen Van Gorchum 1961–63 p 1595–1596 (15 27)

Walsh F B Clinical Neuro Ophthalmology Baltimore William & Wilkins 1957 p 352–353 (14 23 24)

Wise J B MacLean A L & Gass J D M Contractile Peripapillary Staphyloma *Arch Ophthal* (Chicago) 1966 *75* 626–630 (17)

Worton A S Fuch Coloboma and Astigmatism *The Ophthalmoscope* 1911 *9* 833–838 (14 23 24)

Ziering J Der papillare und parapapillare Conus Heterotypicus *Klin Mbl Augenheilk* 1936 *97* 169–284 (12 14 22 24)

Aetiology 26 30 53
Amaurosis fugax 26
Anisometropia 26
Astigmatism 22 24 42 43 54

Bibliography 102
Bitemporal hemianopia 24 25 46 49 50

Carotis angiography 50
Case reports 59 98
Choroidal mottling 30
  pigment 30
  ring 11
  vascular deficiency 20 21 45
Craniotomy 50
Crescent 12 15 43 44 54
  congenital 12
  genetics 19 53
  heterotypical 12
  inferior and nasal 14
  myopic 12
  senile 12

Definition 11
Dysversion of the optic nervehead 15 17 44 54

Ectasia of the fundus 17 21 45 54
  depth examination 17 21 47 49
Electro encephalography 49
Electroretinography 35 49
Exophthalmos 51 54
Explorative craniotomy 50

Fluorecein angiography 20 21
Fuchs coloboma 14
Fundus ectasia 11 17 21 45 47 48

General disease 25 26 37 38
Genetics 9 30 53 56
Glaucoma 26
Headache 49

Hemianopia 24 25
Heredity 30 53 56
Heterotopia macula, 26
Heterotypical crescent 12
Histology 26 28 50

Incidence 36 38
Inferior crescent 14
Inverse myopia 14
Inverse vessel emergence 15 16 44 45

Macular degenerations 26
Methods of examinations 32 35
Migraine, 26
Myopia 21 23 41 42
  congenital 28 30
  degenerations 18 45
  inverse 14

Nasal fundus ectasia 17 21 45
Neuro ophthalmological aspects 49 50 54
Neurosurgical examination, 49 50 54

Occurrence 36 38
Ophthalmoscopy 32 33 43 45 47 54
Other eye disorders 25 26 38 50 52

Pedigrees 56 58
Perimetry 24 25 33 34 46 55
Photographic registration, 32
Pits of the optic disc 26
Pneumo encephalography 50

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SUPPLEMENTUM 127

A K. K. K. LUNDSGAARD EDI COEPTA

Primary Angle-Closure Glaucoma

Oculometry, epidemiology, and genetics in a high risk population

by

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SCRIPTOR COPENHAGEN



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PRIMARY ANGLE CLOSURE GLAUCOMA

Oculometry epidemiology and genetics in a high risk population

By

P H Alsbirk

ABSTRACT

The ocular dimensions in patients suffering from primary angle closure glaucoma (a c g) have been studied in several clinical series chiefly in Caucasians The epidemiology and aetiology of a c g are less well known although genetic factors seem to be involved

Eskimos have recently been shown to constitute a high risk population with respect to a c g Consequently a series of oculometric, epidemiologic and genetic studies among Greenland Eskimos was undertaken Besides the immediate purpose prevention of blindness in this population the survey had important general aspects and the following main results were obtained

1a) Ocular dimensions as well as clinical symptoms in Eskimo a c g patients correspond closely to those of a c g reports from other ethnic groups and *1b*) ocular dimensions of the anterior segment in the general *Eskimo population deviate conspicuously towards the low level characteris*tic of all samples of a c g patients

2) A c g prevalence rates were estimated at 1 6 % in males and 5 1 % in females of the general population aged 40 years or more The epidemiology of a c g seems to reflect closely the variations of axial anterior chamber depth (ACD) according to race (Eskimo Caucasian) sex and age Empirical a c g risk estimates depending on the ACD value were obtained in elderly females

3) A relatively shallow chamber was found in 1st and 2nd degree relatives of a c g patients in close agreement with an earlier study in Caucasians (Tornquist 1953) However also in the general Eskimo population a pronounced familial resemblance with respect to ACD and corneal diameter was found Thus the family studies indicate that the size of the anterior chamber shows a mainly genetic determination which probably constitutes the genetic basis of a c g as well

With this background a hypothesis is discussed which interprets the small anterior chambers in Eskimos as a result of genetic adaptation to arctic environment Corneal protection may have been the significant advantage and the a c g load in elderly persons a relatively less important cost

Key words angle closure glaucoma – anterior chamber depth – corneal diameter – lens thickness – lens position – axial length – epidemiology – polygenic inheritance – heritability – Eskimos

Primary angle closure glaucoma is a serious eye disorder tending to result in blindness The remarkable clinical picture of acute congestive attacks has been known through centuries (cf Lowe 1965) A refined pathogenetic understanding however has been obtained quite recently The old clinical observations of small and shallow anterior chambers in acute glaucoma made by e g von Graefe (1857) Czermak (1897) Priestley Smith (1887 1910–1912) and others have now been confirmed and elaborated in details through gonioscopic and oculo metric investigations (cf below) Consequently in 1955 a glaucoma symposium headed by Duke Elder advocated the use of closed angle glaucoma as the appropriate term of this whole entity among the primary glaucoma diseases Apart from the minor change into angle closure glaucoma the gonioscopic classification has now been widely accepted However until recently some confusion has prevailed within the whole field of primary glaucomas because gonioscopy did not become clinical routine until the 1960 es

The development of *oculometry* through optical and ultrasonographic methods has been of paramount importance to the increasing understanding of the marked *dimensional characteristics of eyes suffering from a c g* (e g Priestley Smith 1890 Raeder 1923 Rosengren 1931 Sugar 1941 Tornquist 1956 1957 1959 Aizawa 1960 Grieten & Weekers 1962 Ortlepp 1966 Delmarcelle et al 1969 Lowe 1969 1970b 1972b 1975 Storey & Phillips 1971) Step by step it has been demonstrated that a c g occurs almost exclusively in eyes with *shallow anterior chambers* due to 1) anteriorly sited *lenses* of 2) increased size and 3) steepness of anterior curvature while 4) small *corneas* (of slightly increased curvature) in 5) axially *short* mostly *hypermetropic eyes* also contribute to the shallowness These ocular dimensions however represent more or less pro nounced mutually correlated deviations within the unimodal distributions of these parameters in the population The conspicuous influence of *age* upon the size and less pronounced the position of the lens (e g Lowe 1970a) gradually reduces the central and peripheral depth of the anterior chamber throughout adult life The trigger mechanisms which via a relative pupil block of aqueous flow finally force the peripheral iris of the narrow chamber angles into apposi tion against the trabecular meshwork are still poorly understood (Mapstone 1968 Wyatt & Ghosh 1970 Lowe 1972a) However peripheral iridectomy seems

to establish a simple and effective surgical protection against the valvelike stoppage of the outflow system (Curran 1931 Barkan 1938 Chandler 1952 Lowe 1973b)

The shallowness of the anterior chamber is effectively gauged by measurement of the axial *anterior chamber depth* (*ACD*) In Caucasian and Japanese clinical series of a c g patients very low ACD values have been found repeatedly since the observations made by Raeder (1923) and Rosengren (1931) However the relationship between the occurrence of a c g and the ACD variation in un selected population groups has not been thoroughly investigated before

The global *epidemiology of a c g* is not well known Most of the a c g studies published so far have been based on clinical series and even in Caucasian populations the incidence or prevalence is largely unknown

However indirectly some epidemiologic information is available. The ratio between cases of simple glaucoma (open angle glaucoma = o a g) and a c. g has been studied in clinical series by several authors Duke Elder & Jay (1969) surveyed these reports and concluded that the o a g./a c g ratio is about 4/1–5/1 in most *Caucasian* series The large number of tonometry mass screenings undertaken since 1950 have revealed primary glaucoma or o a g prevalence rates ranging from 0.5–10 ‰ in the various elderly population groups examined with a prevalence of 1–2 ‰ above the age of forty as a rough representative estimate, which more or less also includes ocular hypertensives (cf survey by Leydhecker 1973) Considering such results together an a c g prevalence of maximum 0.5 ‰ in Caucasians above 40 years might if somewhat rashly be inferred. However using restricted diagnostic criteria in a proper population study Hollows & Graham (1966 in Wales) reported 0 6 ‰ as the combined primary glaucoma prevalence and 0 09 ‰ (4/4608 persons) as the prevalence of a c g Thus most probably *only about one per thousand elderly Caucasians suffer from a c g* although great variation seems to exist The above mentioned o a. g./a c g ratio agrees well with Danish reports (Corydon Andersen 1958 (clinical series) and Norskov 1968 (regional survey of blind ness)) In Iceland the ratio was found to be 14/1 (Bjornsson 1967) possibly influenced by a high frequency of pseudoexfoliation. The ACD level was found to agree with other Caucasian series (Forsius et al 19 4) On the other hand, an outstanding glaucoma clinic survey from London revealed an o a g./a. c g ratio < 1/1 (Smith 1958) Lowe (1963) demonstrated that Italians and Greeks were relatively underrepresented compared with English immigrants in Australian a c g series

Mongoloids seem to show an o a g /a c g ratio far below 1/1 judged by Ida Mann s survey (1966) Loh (1968) and others (cf (3) Alsbirk 1970) Unfortunately no compara tive ACD population studies including Mongoloids have so far been published Among *Negroes* a c g is mostly said to be less frequent than in Caucasians Especially the acute attacks of a c g are rare (Alper & Laubach 1968 American Negroes Luntz 1973 South African Bantus) Olurin (1975) has recently reported that the ACD level of Nigerians corresponds to that of Caucasians Clemmesen & Luntz (1976) found a rela tively th n lens in Bantus compared with Danes as a possibly modifying factor also in a c g In *Australian aborigines* a. c g has not been observed so far a level of ACD as in Caucasians was recently reported (Murchland & Edwards 1975)

Lowe (1973a) recently surveyed the geographical and racial variations of a c g He stated that our present knowledge is very limited and emphasized

that ACD measurements ought to be an integral part of epidemiologic studies in a c g

The *aetiology* of a c g seems to be complex Only a few studies have so far considered the genetic influence upon a c g together with its underlying morphology (e g Tornquist 1953 Paterson 1961 Tomlinson & Leighton 1973) As to ocular dimensions in general some information has also been obtained through family studies of refractive components (e g Steiger 1907 Wibaut 1932 Sorsby et al 1966 Nakajima et al 1968 Young & Leary 1972) Such studies as well as numerous pedigrees (cf Westerlund 1947) have indicated a more or less pronounced genetic component in the aetiology of a c g Irregular autosomal dominant inheritance has mostly been suggested Lately Lowe (1972a) has proposed a polygenic mode of inheritance with a threshold effect as a more likely model

To summarize the *oculometry* of a c. g is fairly well known but chiefly from Caucasian clinical series However even in European populations the *epidemiologic pattern* seems to be fairly obscure and the nature of the suggested *genetic influence* requires further elucidation The discovery of Eskimos as a high risk population with respect to a c g (cf below) gave an important and valuable opportunity further to investigate these problems and to check the current concepts of a c g

Before the present survey a tonometric and gonioscopic population study had been made in Umanaq of West Greenland (71° n. l.) because of a series of acute glaucomatous attacks in elderly females (Alsbirk 1970). Based on a subsequent gonioscopical evaluation (Clemmesen 1971) of 109 patients suffering from primary glaucoma it could be stated that 86 % had primary angle closure glaucoma (o.a.g./a.c.g. ratio 1/6) (Clemmesen & Alsbirk 1969, 1971a) and the overall prevalence of a.c.g. in Greenland was estimated at 2.1 % in females and 0.9 % in males over the age of forty. With the background outlined in the introduction these initial findings motivated a study of the following problems:

1a) Do the *ocular dimensions in Eskimo a.c.g. patients* agree with those of a.c.g. patients from other ethnic groups?

1b) Do the *ocular dimensions in the general Eskimo population* deviate towards the levels of a.c.g. patients?

2) Is there any close association between the *epidemiologic findings* and the ocular dimensions in this high risk population?

3) Are *genetic* or *environmental factors* of major importance to the *aetiology* of a.c.g. and its underlying morphology?

Main results

The more important results of relevance to these problems are summarized below. Details have been given recently in eight papers which are listed on p. 26 and referred to by their numbers below (italicized in brackets).

1a) *Oculometry in Eskimo a.c.g. patients*

In 60 Eskimo a.c.g. patients the axial *anterior chamber depths* (*ACD*) were measured by means of a precise optical method (*4*). They were gonioscopically and *clinically classified* as suffering at the detection from latent (4 patients), intermittent (24), acute (17) or chronic (15) a.c.g., but no variation in ACD according to this subdivision could be disclosed. The overall ACD mean value in the sample was 1.80 mm with standard deviation 0.24 mm and range 1.19–

2 33 mm in close agreement with reports from other ethnic groups (Caucasians Japanese cf Table VII in (5)) As to *corneal diameter* (*CD*) low mean values and agreement with other a c g samples were likewise obtained (7)

The ultrasound oculometry pattern of Eskimo a c g patients is shown in Fig 1 compared with a sample of Caucasian a c g patients ((*1*) Lowe 1970b) Three trends are illustrated Firstly the Eskimo a c g patient mean values show that *ACD* as well as the *mid lens depth* (*MLD* the distance from back of cornea to axial midpoint of the lens) and *lens thickness* (*LT*) agree closely with Caucasian a c g mean values whereas slightly longer *axial lengths* (*AL*)

Fig 1

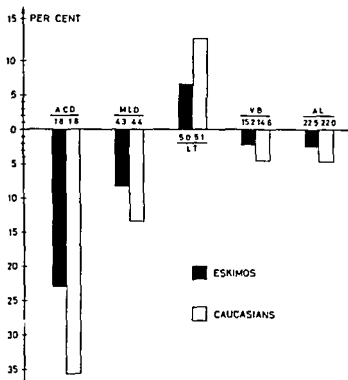
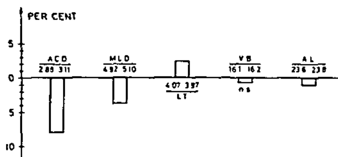


Fig 2



were found in Eskimos Secondly the oculometric deviations in the a c g patients (the vertical bars) are relatively more pronounced in the anterior segment of both ethnic groups and appear massively in the ACD bars Thirdly all Eskimo a c g deviations are considerably smaller than in Caucasians a finding which will be further dealt with below Thus although the limited a c g sample calls for some caution there is apparently oculometric agreement between Eskimo and Caucasian a c g patients as well as clinical similarity (Clemmesen & Alsbirk 1971a)

1b) Oculometry in the general Eskimo population

Gonioscopic screening and ACD measurements in unselected population groups were the first steps in this part of the study cf Fig 3 (Clemmesen & Alsbirk 1971a and (*1*)) ACD was measured using the optical method (*5 4*) in a sample of 1570 Eskimos They were living in one district in East Greenland and five in West Greenland and constituted 93 % of the census populations in selected age and sex groups Together with similar measurements performed in smaller groups of Alaskan and Canadian Eskimos (Young & Leary 1971 Drance et al 1973 Alsbirk & Forsius 1973) the *relative shallowness of the anterior chamber in all Eskimos* was firmly established as an important characteristic of this ethnic group (*3*) The corneal diameter survey in Greenland Eskimos revealed a correspondingly *small-sized cornea* about 0 5 mm below Caucasian control mean values Fig 2 illustrates a comparison between Danes and Eskimos using the same parameters as in Fig 1 The Eskimos were randomly selected from the general population sample (613 adults aged 15+) to

---

Fig 1

Axial ocular dimensions in primary angle closure glaucoma (a c g) Mean values from 29 Eskimo a c g patients and 61 Caucasian a c g patients (Lowe 1970b) are given in mm for five parameters *ACD* anterior chamber depth (excl corneal thickness) *MLD* mid lens depth (= ACD + ½ LT) *LT* lens thickness *VB* vitreous body length and *AL* axial length (incl corneal thickness) *Percentual mean value deviations are illustrated by vertical bars (a c g patient mean value minus control mean* value in per cent of the latter) The control samples included 58 Eskimos and 80 Caucasians (Lowe 1970b) respectively selected to match the a c g samples according to age and sex n s * ** and * indicate not significant $P < 0.05$ < 0.01 and < 0.001 respectively by a *t* test comparison of patients and controls (unpaired two tailed) (VB values were not given by Lowe (1970b) but could be calculated)

Fig 2

Axial ocular dimensions in Eskimos and Danes (matched according to age and sex without a c g) *Mean values* of 70 Eskimos (first value) and 70 Danes (second value) are given in mm for five parameters *Percentual mean value deviations* of Eskimos are illustrated by vertical bars (Eskimo mean value minus Dane mean value in per cent of the latter) Abbreviations and symbols as in Fig 1

2 33 mm in close agreement with reports from other ethnic groups (Caucasians Japanese cf Table VII in (5)) As to *corneal diameter* (*CD*) low mean values and agreement with other a c g samples were likewise obtained (7)

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Fig 1

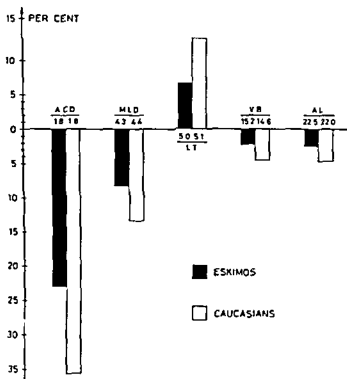
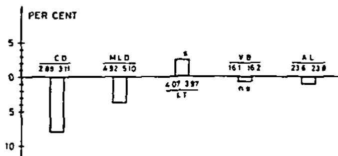


Fig 2



because of symptoms was fairly low 54 years (range 36–72) compared with Caucasian series (e g Lowe (1975) mean age 64 years) A corresponding relationship between a c g occurrence and ACD distribution according to *race* and *sex* was demonstrated For the first time this study permitted an empirical estimate of a c g prevalence according to different ACD levels within a given population ((5) Table V and (6) Table II) As expected according to theory (cf the introduction) a steep increase in a c g prevalence through the lower levels of ACD was found An ethnic comparison between a c g prevalence in Eskimos (Drance 1973a (5)) and in Caucasians (Hollows & Graham 1966) revealed roughly a 40/1 ratio between these populations Törnquist s control sample (1953) of 398 Swedes enabled me to calculate the relative number of persons to be expected in a Caucasian population at different levels of ACD When compared with similar Eskimo frequencies the 40/1 a c g prevalence ratio seemed to agree remarkably well with the ratio between no of general population Eskimos versus Caucasians within the range of low ACD values characteristic of a c g patients ((5) Fig 2) The sex difference of ACD (0 16 mm (2)) was analysed in a similar way and proved to show a corresponding agreement with the 3/1 a c g prevalence ratio (♀/♂) observed in this and most other studies

3) Genetic studies in a c g families and general population families

The a c g prevalence in sibs as well as the future expected prevalence in sibs and children of a c g probands was estimated and a moderate increase (x 3 5) was demonstrated (6) However the limited material and especially the age influence made it difficult to perform a reliable Mendelian analysis based on *qualitative* data On the other hand the conspicuous dimensional pattern in a c g pathogenesis confirmed also in Eskimos enabled the use of a different approach based on the theory of *quantitative genetics* (cf Fisher 1918 Falconer 1960 Holt 1968) In this way the biometric information concerning the single individuals could be utilized (cf Smith & Mendell 1974)

As a first step in such a study using the most relevant parameter ACD the conspicuous influence of age and sex had to be accounted for A statistical transformation of the ACD values into positive or negative deviations from the appropriate linear age regression lines was made Further the increasing variance with age (9) was neutralized using the standard deviation from regression (s_y) as a *unit of measurement (6)* A nearly identical approach was used by Armaly (1967) in applanation pressure studies Fig 4 shows the total Eskimo population sample after this *transformation of ACD* into standardized deviation scores so called *DS values* Obviously this distribution must be located around a *mean value of 0 0 with a standard deviation* of 1 0 DS units It appears that a Gaussian distribution could be safely assumed (goodness of fit test χ = 11 5 15 degrees of freedom $P < 0 8$)

The *Swedish family material* described by Tornquist (1953) was treated in an analogous way for purposes of comparison Based on the control group (398 persons aged

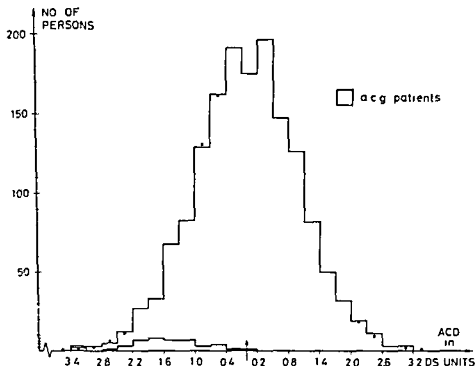


Fig 4

Anterior chamber depth (ACD) distribution of 15 0 individuals following a trans formation into age and sex independent standardized deviation score values (DS) Mean value 0 00 (†) is indicated one standard deviation = 1 DS unit corresponds to 0 30 mm ACD The dots (●) indicate the expected number of persons according to a Gaussian distribution Patients with primary angle closure glaucoma (a c g) within this population are shown

20 35 50 and 65 years) parabolic regression lines were reported for both sexes with an average standard deviation of 0 28 mm By means of the individual data on age sex and ACD given in the appendix the DS values of the probands (suffering from acute or intermittent glaucoma) as well as of their sibs and children were computed (by me) (Tornquist s appendix lists 128 relatives Of these one monozygotic twin and two half sibs all with a c g, and a 12 year old child were excluded for theoretical reasons)

Table I shows a summary of the Eskimo family values obtained (cf (6)) compared to the Swedish material which has not been presented in this way before While the $\overline{DS}$ values of probands and 1st degree relatives are seen to be much lower in Swedes than in Eskimos the corresponding regression coeffi cients (b_{yx}) are almost identical in the two populations This statistical para meter b_{yx} gives a numerical expression of the *degree of resemblance between relatives and probands* With the standardized DS measure applied the theo

Table I

Anterior chamber depth (ACD) as deviation score (DS) in Eskimos and Caucasians (Swedes from Tornquist 1953) DS parameters of the general population and in a c g proband families are shown

Sample		Eskimos					Swedes				
		No of persons	$\overline{DS}$	s_{DS}	b_y	s_b	No of persons	$\overline{DS}$	s_{DS}	b_y	s_b
Population		1570	0 00*	1 00	–	–	398	0 00*	1 00*	–	–
A c g probands	(x)	52	–1 57	0 79	–	–	48	–3 64	0 94	–	–
Full sibs	(y)	49	–0 40	0 96	0 31	0 08	55	–0 79	1 23	0 25	0 05
Children	(y)	143	–0 32	0 94	0 21	0 04	68	–0 80	0 97	0 20	0 03
Total (1st degree)	(y)	192	–0 34	0 94	0 23	0 04	123	–0 80	1 09	0 22	0 03

$\overline{DS}$ mean value of deviation score (DS) s_{DS} standard deviation
b_y regression coefficient s_b standard error of b_{yx} * theoretical values

retical maximum and minimum values of b_y are in the statistical sense ± 1 00 From a genetic point of view these regressions should maximally achieve the value corresponding to the proportion of genes in common i e for example 0 50 in 1st degree relationships (parent offspring sib sib) while b_y = 0 0 signifies no similarity with respect to this dimension and speaks against a genetic determination In Fig 5 these data are illustrated It must be noted that the graph accounts for the difference in population ACD mean values in Eskimos and Swedes which amounts to as much as 0 40 mm = 1 3 Eskimo DS units at the age of 60 years Accordingly the 0 0 point of the Swedish graph is displaced + 1 3 DS units along both Eskimo axes The resemblance between sibs or children and probands judged by the regression lines is seen to be equally great in Swedish and Eskimo a c g families (cf the slopes b = 0 22 and b = 0 23 respectively) *In both ethnic groups the sibs and children of a c g patients are seen to have significantly lower mean values than the general background population* (cf the relation between vertical 95 % confidence limit arrows and the horizontal zero lines)

Thus the Tornquist study received substantial support from this material obtained from a new population with much shallower anterior chambers Moreover various second degree relatives corresponded with this finding (6) How

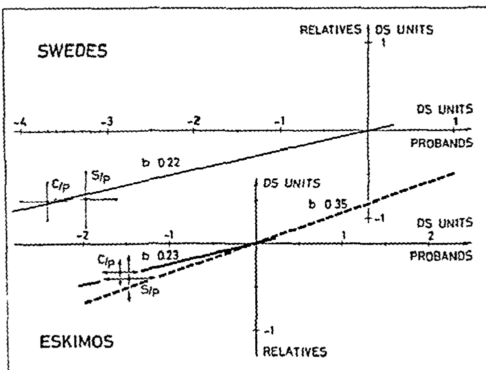


Fig 5

Family distributions of ACD (as DS values cf Table I Fig 4) in sibs (S) and children (C) of a c g probands (P) indicated two dimensionally by 1) mean values and 95% confidence limits (—┼—) as well as 2) the pooled regression lines through 0 0 (for S & C on P relationships) (———) Furthermore the figure shows the regression line of general population Eskimo families (- - - - -) based on 564 child parent relationships (8) Regression coefficients (b) are given (The Swedish system of DS coordinates is displaced two dimensionally according to the ethnic difference between ACD mean values at the age of 60 0 40 mm = 1.3 DS units)

ever the large number of complete Eskimo families examined permitted the ACD family resemblance to be gauged *also in families of the general population* These analyses showed convincingly that not only shallow chamber probands (without a c g (6)) but also probands selected from the whole range of chamber depths tend to show a corresponding similarity with their offspring and their sibs (8) Thus Fig 5 also includes the overall child on parent regression line through the whole range of proband DS values (b = 0 35) As this slope is even higher than in a c g families it can be *concluded* that *the familial resemblance with respect to anterior chamber depth (ACD) is a general pattern and not a particular phenomenon in a c g families*

In the genetic papers (6 8) it is described that such regression studies accord

ing to the theory of quantitative genetics permit cautious interpretation with respect to the *heritability* of a trait expressed as a positive figure between zero and unity For example the above mentioned b = 0.35 estimate gives the proportion 0 7 out of the theoretical value 0 50 to be expected in 1st degree relationships assuming a fully genetic determination. In nearly all subgroups examined such a heritability (h) estimate of about 0 7 was obtained indicating that about 70 % of the age and sex independent ACD variation may be explained by additive polygenic inheritance A corresponding result was obtained in the more limited family study on corneal size (7) Earlier studies on corneal curvature (e g Steiger 1907 Wibaut 1932 Nakajima et al 1968 Young & Leary 1972) have shown a corresponding pattern Thus a *pronounced genetic influence upon the basic dimensional anatomy of the anterior chamber is indicated*

In conclusion the main problems set out in the above (p 9) could be answered in the following way

1a) The ocular dimensions studied in Eskimo angle closure glaucoma patients agree with those of Caucasian a. c g reports

1b) The ocular dimensions of the anterior segment studied in general population Eskimos deviate conspicuously towards the level characteristic of a c g patients

2) The epidemiology of a c. g in this high risk population seems to reflect the Eskimo Caucasian difference in anterior chamber depth (ACD) as well as the influence of age and sex on this parameter

3) A mainly genetic determination of the dimensional anterior chamber anatomy seems to exist

Acute attacks of primary angle closure glaucoma (a c g) are among the old impressive challenges to ophthalmology Blindness has often been successfully prevented by treatment given in due time but a c g tends to be a disease of procrastination and incorrect diagnosis (Lowe 1961) The first convincing description of a series of acute glaucoma attacks in Eskimos was given by Borresen (1926) who was medical officer in Greenland (district of Godthåb) Among 1250 inhabitants of whom according to census figures scarcely more than 250 were older than 40 years 10 cases were found i e a prevalence of 4 % This fairly unnoticed observation has now received massive support from Greenland and Canada as well (Clemmesen & Alsbirk 1969 1971a Drance 1973a) The frequent a c g occurrence in elderly Eskimos is most probably no new phenomenon

No population studies with regard to a c g have been published before the present surveys in Greenland Eskimos (Armaly 1975) Admittedly Eskimos constitute but a very small minority of mankind and historically their environmental background has been among the most extreme However clinical experience as well as gonioscopic and oculometric findings showed at an early stage that the generally accepted nosography of a c g also applies to Eskimo a c g patients The well known clinical entity of a c g seems to prevail only the high frequency is unusual

Thus the surveys among Greenland Eskimos were undertaken with a double purpose Firstly the efforts aimed at prevention of blindness within this limited population Secondly it was felt that valuable contributions of general significance could be obtained in particular through a study of a high risk population The a c g challenge to local health authorities with their very limited access to expert ophthalmic assistance has been discussed in detail elsewhere (Clemmesen & Alsbirk 1971a Clemmesen 1973a b Drance 1973b) In the following it is chiefly the general aspects of the present findings concerning oculometry epidemiology and genetics in a c g that will be discussed As a great advantage in relation to both purposes described above Greenland Eskimos were found to be willingly cooperative and thus high participation rates were generally obtained

Oculometry and epidemiology in a c g The axial *anterior chamber depth (ACD)* was studied extensively as the most important measurable dimension in a c g development (cf the introduction and (2 3 4)) Evidently the ACD value provides only indirect information on the narrowness of the angle in the chamber periphery or the conditions at the pupillary border around which the disordered physiology of the aqueous flow occurs during pupil block and subsequent angle closure However so far no other easily prac ticable quantitative approach seems to exist and the importance of ACD measurements has been repeatedly emphasized by the results of several in vestigators (e g Rosengren 1931 Tornquist 1956 Lowe 1970b Storey & Phillips 1971 Tomlinson & Leighton 1973) Furthermore the optical measure ment using modern equipment is precise and fully acceptable to all persons in a population study (4)

The close association between a c g and ACD was substantially supported by the present results From an epidemiological point of view the estimation of the *a c g risk at different levels of ACD* was an important result of the study Such empirical risk estimates have not been obtainable in other popula tions before In agreement with Törnquist (1956) and Lowe (1972a) no a c g patient was found with ACD above 2 5 mm Through the intervals 2 5–2 0 2 0–1 5 and below 1 5 mm prevalence rates of about 1 %, 20 % and 85 % respectively were found (cf 5) For elementary physiological reasons future studies might possibly show that such risk estimates according to the (axial) ACD level roughly apply also to other populations The narrow space be tween anterior lens surface and corneal endothelium of a human eye must show a certain minimum (peripheral) depth in order to allow a free aqueous flow along the back and front of the iris membrane with its inter and intra individual variations in position structure and thickness The *sexual* and *ethnic differences* in a c g prevalences encountered in this study corresponded remarkably well with the difference in ACD distributions (cf Fig 2 in (5)) As to *age* the same agreement was found The *age influence upon a c g and ACD* bears an epidemiological aspect which is no less important in a popula tion with shallow chambers (5) The regression coefficient of ACD on age (= annual decrease) was found to be –0 015 mm/year in all adults (above 15 years (2)) slightly smaller in the elderly age groups (aged 40+) –0 010 mm/ year (3) Thus the future level of ACD at higher ages should be roughly predictable if the actual ACD value of an individual is known

A correspondingly close *association between a c g epidemiology and the variation in other ocular dimensions* probably does not exist Thus in *corneal diameters (CD)* a weaker relationship was found although it was shown that the whole Eskimo population studied had nearly as small mean CD values as those reported in various samples of a c g patients ( ) As Fig 1 suggests the *mid lens depth (MLD)* would probably also be of smaller discriminative value than ACD The *relative lens position* in a c g

patients i e MLD = ACD + ½ LT taken as a proportion of the axial length (AL) showed a relatively smaller deviation than MLD itself MLD/AL mean ± sr 0 192 ± 0 002 in a c g patients versus 0.204 ± 0 002 in controls (difference 6 % of the latter $P < 0\,001$) Lowe (1969) who introduced this parameter reported the mean values 0 20 and 0 22 respectively which gave a highly significant difference of 9 % As to the overall eye ball size almost the same *axial length* averages were found in Eskimos and in Danes (cf Fig 2) although the standard deviation was larger in the latter group which showed a higher proportion of myopes (sn 1.34 mm AL in Danes versus 0 88 mm in Eskimos F = 2 3 $P < 0\,01$) Correspondingly the *corneal radius (CR)* survey briefly mentioned in (4) showed no significant difference between Eskimos and Danes One aspect of corneal curvature however deserves further study McLenachan & Loran (1967) demonstrated an increased frequency of inverse astigmatism in a c g patients In fact as frequently reported *inverse astigmatism* is a very common condition in Greenlanders (Normann Hansen 1911 Hertz 1929 Lawetz 1949 Skeller 1954) However Forsius & Eriksson (1973) concluded surprisingly that this refractive error is not due to corneal refraction Eskimo *refraction* has recently attracted considerable attention (Young et al 1969 Morgan & Munro 1973 Alsbirk & Forsius 1973 Wyatt et al 1974 Morgan et al 1975) as an epidemic of myopia in adolescents seems to have developed in Alaska and Canada On the other hand Skeller (1954) has reported a very low frequency of myopia in pure East Greenland Eskimos However none of these findings seem to apply to West Greenlanders (Hertz 1929 Lawætz 1949 Skeller 1949 Alsbirk & Forsius 1973) and the distribution of refractive errors in this population will have to be clarified by further studies

In summary it was apparent from the oculometric studies that a c g epidemiology in this population corresponded closely to the ACD variations Related anterior segment parameters showed weaker associations On the other hand axial length and corneal radius in Eskimos and Caucasians were found to be similar

Evidently a number of other *qualitative* conditions interact with the dimensional factors underlying a c g The *gonioscopic appearance* of the chamber angle is of paramount importance (e g Sugar 1941 Barkan 1954) Gonioscopy in Eskimos has been described by Clemmesen (19 1 1973b) Drance et al (1973) and Clemmesen & Alsbirk (19 1a) In Fig 3 a marked association between (low) ACD and narrowness of the chamber angle is illustrated The peripheral chamber depth was studied by Tornquist (1953) and Aizawa (1960) who found significantly lower values in a c g patients compared with shallow chamber control persons without a c g The *plateau iris syndrome* is found in a small minority of Caucasian a c g patients with an anteriorly inserted iris (Becker & Shaffer 1965) In such patients the axial ACD does not necessarily show a low value So far no Eskimoan cases have been reported. Clemmesen reported as a surgical experience based on 60 iridectomies in Greenland Eskimos that their *irides are thicker and more substantial* than those of Europeans (Clemmesen & Alsbirk 19 1b) Suzuki & Kitazawa (1974 from Japan) reported significant variations *of the iris crypt pattern* in primary glaucoma with fewer crypts in a c g than in o a g cases *Pseud exfoliation* of the anterior lens capsule is not a frequent phenomenon in a c g (Lowe 1964) On the other hand this condition shows a remarkable association with o a g (cf Aasved 19 1) and has attracted considerable attention in North European populations (Aasved 1969 Forsius et al 19 4) However in Eskimos a population study of 149 persons above 40 years showed no cases of pseudoexfoliation (Forsius &

Luukka 1973) In *cataracteous eyes* ACD may be influenced in both directions Del marcelle & Luyckx Bacus (1971) showed that the increase in lens thickness and shallowing of the chamber with age is stopped when cataract supervenes i e in non intumescent cataracteous eyes a relatively deep chamber is found On the other hand intumescent cataract is obviously one of the important causes of *secondary angle closure glaucoma* A shallow chambered eye must be considered as highly predisposed to this and most of the other types of secondary a c g Thus Drance (1973a) classified 5/16 of his Eskimo a c g patients as such and correspondingly Greenlanders with secondary glaucoma are no rarity (e g 5/396 = 1 % of persons over 40 years in the Umanaq survey (*1*))

Heredity The genetic contributions obtained have been discussed at length (*6 8*) The full agreement between Eskimo and Swedish a. c g families in spite of the different ACD levels of the populations (Table I Fig 5) is a new remarkable result of the survey The interpretation of such results however within the field of quantitative genetics is not unambiguously accepted (cf Cavalli Sforza & Bodmer 1971) Nevertheless in the present study the heritability estimates obtained appeared to be fairly consistent through various subgroups (*6 8*) Thus the *dimensional anatomy of the anterior chamber shows a mainly genetic determination which probably must be due to polygenes* Significant *non genetic* factors were not clearly demonstrated in the study but it is obvious that random errors of measurement minor diurnal fluctuations of ACD and minor influence of accommodation during the ACD measurement (*4*) must all have contributed to the non genetic part of the variation Furthermore a small inevitable number of erroneous paternities must have lowered the correlations which nevertheless were generally higher in father child than in mother child relationships (*8*) Thus the *truly environmental factors influencing the anterior chamber are still obscure* but seem to be of much smaller importance than genetic factors However polygenic traits are known to show a considerable plasticity Common environmental factors influencing the ACD level of the whole population may exist This is convincingly emphasized for example by the secular trend in a characteristic as human body stature Correspondingly Canadian Eskimo adolescents now seem to have a relatively high ACD level associated with their remarkable epidemic of myopia (Drance et al 1973 Alsbirk & Forsius 1973 (*3*)) which must be due to environmental factors (Morgan et al 1975) However on the basis of the present results from Greenland Eskimos the *occurrence of a c g seems mainly to depend on the polygenic determination of anterior chamber dimensions* As Fig 5 illustrates sibs and children of a c g probands show a lower ACD level and thus run a higher risk of developing a c g than the general population

As in other polygenic disorders associations between a c g and monomeric polymorphic traits could possibly be shown to exist indicating a major allelic influence within the genetic determination Thus Kubičkowa et al (1972) have demonstrated a

low frequency of blood group A individuals among Caucasian a c g patients Correspondingly Becker & Morton 1964 demonstrated a *low phenylthiourea (PTC) nontaster frequency* among American White and Negro a c g patients However this finding was not confirmed by Kubíčková et al (1972) or Kalmus & Lewkonia (1973) Furthermore *the PTC survey in Umanaq Eskimos (Alsbirk & Alsbirk 1972) showed no correlation between nontaster frequency and ACD* Nevertheless other similar mono or *polygenic relationships may well exist Thus an association between body stature and ACD* was disclosed in a subgroup of the present material (8) and this relationship seems to account for most of the sex difference observed in ACD

Evolutionary aspects Judged by the present results the shallow anterior chamber is a distinct mainly genetically determined feature in Eskimos What *is the reason of such a characteristic which implies an increasing risk of* blindness from the age of forty in some per cent of the Eskimo population?

Lowe who considers a c g as a polygenically determined multifactorial disease *(1972a) has recently advanced this philosophical note Man has the most efficient* eye of the mammals permitting an accurate range of focus from very near to infinity *(-) But in all evolution some individuals have to pay a price and so pupilblock angle* closure glaucoma appears to be one cost some people have to pay that all may benefit *from having a focusing lens delicately slung behind the pupil in the stream of aqueous* flow (1975)

An analogous evolutionary idea implying *genetic adaptation to cold environments* seems to emerge from the present findings in Eskimos the arctic specialists of mankind Vision requires passage of light to retina through a *number of avascular potentially cold structures as cornea aqueous of the* anterior chamber lens and vitreous body The heat regulation and nutrition of these tissues depend fundamentally on blood vascular circulation of the limbus iris and ciliar body Cold injuries or other climatic strain of the eye are generally irrelevant to everyday clinical work in urbanized communities However the evolution of man has taken place under highly different conditions and this is true in particular of Eskimos

The *climatic impact* upon the eye in Eskimos has attracted attention from the first contact with Europeans Thus snowblindness pterygium pinguecula and climatic droplet keratopathy have been described several times cf e g the survey by Berthelsen (1940) Freedman (1965 1973) Wyatt (1973) and Young & Finlay (1975) As to *acute injuries caused by cold and wind* Forsius (1972) observed acute changes of the corneal epithelium among snowscooter drivers from Igloolik in the Canadian Arctic and similar findings were made in Norway by Kohlstad & Opsahl (1969) in cross country skiers A few casuistic reports are summarized by Duke Elder & MacFaul (1972) From Greenland Freuchen (1915) who lived among the Thule polar Eskimos reported that - many kajak hunters and others are lost in the winters due to freezing of the eyes with sudden impairment of vision *In Umanaq I have observed a severe bilateral corneal c ngelat i* tainable with fluorescein in a 62 year old Eskimo who suddenly *got severely blu d vision when striving against the cold wind a february afternoon* pulling a seal behind him over the ice He was luckily found still alive and walking

24 hours later – For the lonely arctic hunter corneal congelation has obviously been a perilous condition

Experimental evidence was reported by Brændstrup (1952) She showed that mid *corneal temperature* was on an average 32 0 C slightly lower than the limbal (32 4) and conjunctival fornix temperatures (35 4°) The most conspicuous variation observed was due to the rather mild cold stress of one hour s outdoor walk in –1.5 C This very slight exposure gave a corneal temperature 11° below the indoor value Rysa & Sarvaranta (1974a b) reported that the immediate decrease of corneal temperature was faster in eyes with shallow ACD values than in eyes with deeper chambers through the first few minutes in a climate room at –15 C (n = 20 eyes) A secondary rise was observed after 10 minutes followed by a slower fall through an observation period of 45 minutes and no ACD association was observed at this time However clinical experience and Brændstrup s observation suggest that the natural variability of corneal temperature must be very much larger than Rysa & Sarvaranta s results have so far shown In long term major cold stress situations it seems hardly possible that a deep chamber could be advantageous with respect to maintenance of corneal temperature. As described by Brændstrup (1952) the *highly vascular ciliary body and iris* might be looked upon as the *heating elements of the anterior segment and its window the cornea* It seems to be a plausible idea that Eskimos if any may show an adaptation of the ocular anatomy to cold environments (cf Harvald 1979) The *anatomy of the external eye in Eskimos* with narrow palpebral fissures and pronounced Mongol or Eskimo eyelid folds (Skeller 1954) may have *a correlate within the eyeball* through the small anterior chambers Obviously a number of *other variables* may also be significant e g the corneal sensitivity (Kolstad 1970) which shows ethnic variations (Millodot 1975) the rate of blinking the amount of tear flow as well as facial morphology growth of beard etc In the hybrid population of West Greenland the more pronounced Eskimoan physiognomies showed the lower ACD values and corneal diameters (8) After all it seems highly relevant to include ocular variables in experiments which try to explain ethnic variations of facial morphology in adaptative terms (cf Steegman 1970 1972)

Natural selection against deep anterior chambers with large corneae may have been an active force through the several thousand years of arctic life According to this idea the advantage to hunters i e the males of small and well protected corneas should have been the most significant factor However indirectly females and children would benefit as well since the whole family was vitally dependent on the hunter s yield which among other qualities requires a sharp vision The predisposition to a c g which mainly loads Eskimo females because of their slightly shallower chambers might be looked upon as a *cost to be paid for an otherwise positive genetic adaptation* but a cost of very small selective significance as a c g practically does not occur during fertile life

In conclusion the oculometric and epidemiologic results of the present study indicate that the high prevalence of primary angle closure glaucoma (a c g) in Eskimos is a consequence of their particularly small anterior chambers This quantitative anatomical trait has a mainly genetic basis The findings seem to suggest genetic adaptation to arctic environments as a relevant explanatory hypothesis

The studies here surveyed were carried out in 1969–1975 while I was employed in the Health Service Umanaq Greenland the University Eye Clinic Rigshospitalet Copenhagen and the University Institute of Clinical Genetics Odense

Nearly two thousand Greenland Eskimos participated in the population studies Their kind and cheerful cooperation formed the basis for the whole project and was an unforgettable experience Further a hundred Danes in Umanaq willingly took part

From the beginning Viggo Clemmesen M D has been the most active ophthalmological consultant of the project No other eye specialist has achieved his personal experience in ophthalmic care in Greenland Through several journeys and an endless number of letters and discussions he has actively supported the project through all phases I am also grateful to Professor Poul Brøndstrup M D and Professor Bent Harvald M D who have given significant inspiration in the planning of the project

During the practical phases indispensable support was given by the health service personnel in seven districts backed up by the Chief Medical Officer in Greenland Thanks are especially due to Eva Steenstrup head nurse in Umanaq who has given large and dedicated work I thank my wife Ida Alsbirk ophthalmic assistant for extensive help and support and also my brother Dr Knud Erik Alsbirk

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Holte March 1976 *Poul Helge Alsbirk*

The present article surveys the following eight papers referred to by italicized numbers (in brackets) The nine publications are the author s thesis

(1) Alsbirk P H *(19 3)* Angle closure glaucoma surveys in Greenland Eskimos A preliminary report *Canad J Ophthal 8* 260–264

(2) Alsbirk P H (1974a) Anterior chamber depth in Greenland Eskimos I A population study of variation with age and sex *Acta ophthal (Kbh) 52* 551–564

(3) Alsbirk P H (1974b) Anterior chamber depth in Greenland Eskimos II Geographical and ethnic variation *Acta ophthal (Kbh) 52* 565–580

(4) Alsbirk P H (1974c) Optical pachymetry of the anterior chamber A methodological study of errors of measurement using Haag Streit 900 instruments *Acta ophthal (Kbh) 52* [illegible]

(5) Alsbirk P H (1975a) Anterior chamber depth and primary angle closure glaucoma I An epidemiologic study in Greenland Eskimos *Acta ophthal (Kbh) 53* 89–104

(6) Alsbirk P H (1975b) Anterior chamber depth and primary angle closure glaucoma II A genetic study *Acta ophthal (Kbh) 53* 436–449

(7) Alsbirk P H (1975c) Corneal diameter in Greenland Eskimos Anthropometric and genetic studies with special reference to primary angle closure glaucoma *Acta ophthal (Kbh) 53* 635–646

(8) Alsbirk P H (1975d) Anterior chamber of the eye A genetic and anthropological study in Greenland Eskimos *Human Heredity 25* 418–427

Other references

Aasved H (1969) The geographical distribution of fibrillopathia epitheliocapsularis so called senile exfoliation or pseudoexfoliation of the anterior lens capsule *Acta ophthal (Kbh) 47* 792–810

Aasved H (1971) The frequency of fibrillopathia epitheliocapsularis (so called senile exfoliation or pseudoexfoliation) in patients with open angle glaucoma *Acta ophthal (Kbh) 49* 194–210

Aizawa K (1960) Studies on the depth of the anterior chamber *Jap J Ophthal 4* 272–286

Alper M G & Laubach J L (1968) Primary angle closure glaucoma in the American Negro *Arch Ophthal 79* 663–668

Alsbirk K E & Alsbirk P H (1972) PTC taste sensitivity in Greenland Eskimos from Umanaq Distribution and correlation to ocular anterior chamber depth *Human Heredity 22* 445–452

Alsbirk P H (19 0) Primary glaucoma in Greenland (Umanaq district) I Introduction The normal intraocular pressure *Acta ophthal (Kbh) 48* 1061–1079

Alsbirk P H & Forsius H (19 3) Anterior chamber depth in Eskimos from Greenland Canada (Igloolik) and Alaska (Wainwright) A preliminary report *Canad J Ophthal 8* 265–269

Andersen O Corydon (1958) Die Haufigkeit des Glaukoms *Acta ophthal (Kbh) 36* 6 2–650

Armaly M F (1967) Age and sex correction of applanation pressure *Arch Ophthal 78* 480–484

Armaly M F (1975) Glaucoma Annual review *Arch Ophthal 93* 146–162

Barkan O (1954) Primary glaucoma Pathogenesis and classification *Amer J Ophthal 37* 24–44

Becker B & Morton W R (1964) Phenylthiourea taste testing and glaucoma *Arch Ophthal 72* 323–327

Becker B & Shaffer R. N (1965) *Diagnosis and Therapy of the Glaucomas* p 160 2nd ed Mosby St Louis

Bertelsen A (1940) Grønlandsk medicinsk statistik og nosografi *Meddelelser om Grønland 117 (3)* 139–142

Bjornsson G (1967) The primary glaucoma in Iceland. Epidemiological studies *Acta ophthal (Kbh) Suppl 91*

Brændstrup J M (1952) *Ojets kliniske temperatur* Dansk videnskabs forlag A/S København.

Børresen P (1926) Om forekomsten af glaucom og blindhed i Grønland *Ugeskr Læg 88* 194–195

Cavalli Sforza L. L & Bodmer W (1971) *The genetics of human populations* pp 59 –607 Freeman, San Francisco

Chandler P A (1952) Narrow angle glaucoma *Arch Ophthal 47* 695–716

Clemmesen V (1971) Problems in gonioscopic screenings in Greenland Technique, classification of findings diagnosis *Acta ophthal (Kbh) 49* 59–64

Clemmesen V (1973a) Ophthalmic care in Greenland *Canad J Ophthal 8* 234–240

Clemmesen V (1973b) Gonioscopic screenings in Greenland. *Canad J Ophthal 8* 270–273

Clemmesen V & Alsbirk P H (1969) Le glaucome primaire au Groenland *Bull Soc franç Ophtal 82* 243–249

Clemmesen V & Alsbirk P H (1971a) Primary angle closure glaucoma (a c g) in Greenland *Acta ophthal (Kbh) 49* 47–58

Clemmesen V & Alsbirk P H (1971b) The actual glaucoma situation in Greenland Detective therapeutic and preventive measures Paper read at the *Second Congr Int Soc geograph Ophthal* Jerusalem

Clemmesen V & Luntz M H (1976) Lens thickness and angle closure glaucoma A comparative oculometric study in South African Negroes and Danes *Acta ophthal (Kbh) 54* 193–19

Curran E J (1931) Peripheral iridotomy in acute and chronic glaucoma some results after ten years duration Anatomical classification of glaucoma *Trans ophthal Soc U K 51* 520–538

Czermak W (1897) Einiges zur Lehre von der Entstehung und dem Verlaufe des prodromalen und acuten Glaukomanfalles *Prag med Wschr 22* 1–3 15–17 38–40

Delmarcelle Y Luyckx J & Weekers R (1969) Etude biometrique du segment anterieur de l œil dans le glaucome a angle ferme *Bull Soc belge Ophtal 153* 638–6 0

Delmarcelle Y & Luyckx Barus J (1971) Biometrie du segment anterieur dans la cataracte senile *Acta ophthal (Kbh) 49* 454–466

Drance S M (1973a) Angle closure glaucoma among Canadian Eskimos *Canad J Ophthal 8* 252–254

Drance S M (1973b) Glaucoma panel summary The implications on the findings and suggestions for management of angle closure glaucoma in northern communities *Canad J Ophthal 8* 278–279

Drance S M Morgan R W Bryett J & Fairclough M (1973) Anterior chamber depth and gonioscopic findings among the Eskimos and Indians in the Canadian Arctic *Canad J Ophthal 8* 255–259

Duke Elder S (1955) Ed *Glaucoma A symposium* pp 315–316 Blackwell Oxford

Duke Elder S & Jay B (1969) Primary closed angle glaucoma In Duke Elder S *System of Ophthalmology Vol XI* p 564 Kimpton London

Duke Elder S & MacFaul P A (1972) Hypothermal injuries In Duke Elder S *System of Ophthalmology Vol XIV (2)* pp 776–799 Kimpton London

Falconer D S (1960) *Introduction to quantitative genetics* Oliver Boyd Edinburgh

Fisher R A (1918) The correlation between relatives on the supposition of Mendelian inheritance *Trans roy Soc Edinb 52* 399–433

Forsius H (1972) Climatic changes in the eyes of Eskimos Lapps and Cheremisses *Acta ophthal (Kbh) 50* 532–538

Forsius H & Eriksson A (1973) The cornea at northern latitudes Corneal power arcus senilis and corneal scars in Eskimos Lapps and Finns *Canad J Ophthal 8* 280–285

Forsius H & Luukka H (1973) Pseudoexfoliation of the anterior capsule of the lens in Lapps and Eskimos *Canad J Ophthal 8* 274–277

Forsius H Sveinsson K Als E & Luukka H (1974) Pseudoexfoliation of the lens capsule and depth of anterior chamber in northern Iceland *Acta ophthal (Kbh) 52* 421–428

Freedman A (1965) Labrador keratopathy *Arch Ophthal 74* 198–202

Freedman A (1973) Climatic droplet keratopathy I Clinical aspects *Arch Ophthal 89* 193–197

Freuchen P (1915) Om sundhedstilstanden blandt polareskimoerne *Ugeskr Læg 77* 1089–1108

Graefe A v (1857) Ueber die Iridectomie bei Glaucom und uber den glaucomatosen Process *Albrect v Graefes Arch Ophthal 3* 456–555

Grieten J & Weekers R (1962) Etude des dimensions de la chambre anterieure de l œil humain 3 partie Dans le glaucome a angle ferme et dans le glaucome à angle ouvert *Ophthalmologica (Basel) 143* 409–422

Harvald B (1972) Disease prevalence in Greenland *Acta socio medica scand Suppl 6* 203–205

Hertz V (1929) Meddelelser om øjensygdomme i Grønland *Ugeskr Læg 91* 805–806

Hollows F C & Graham P A (1966) The Ferndale glaucoma survey In Hunt L B Ed *Glaucoma Symposium* pp 24–44 Livingstone Ltd London

Holt S B (1968) *The genetics of dermal ridges* Thomas Springfield Illinois

Kalmus H & Lewkonia I (1973) Relation between some forms of glaucoma and phenylthiocarbamide tasting *Brit J Ophthal 57* 503–506

Kolstad A (1970) *Corneal sensitivity by low temperatures Acta ophthal (Kbh) 48* 789–793

Kolstad A & Opsahl R (1969) Cold injury to corneal epithelium A cause of blurred vision in cross country skiers *Acta ophthal (Kbh) 47* 656–659

Kubičková Z Klouček F Kraus H & Dvořaková M (1972) Blutgruppen des ABO Systems Sekretorstatus und PTC Schmecken bei Glaukomkranken *Klin Mbl Augenheilk 161* 3?–35
Lawætz B (1949) Undersogelser af grønlændernes øjensygdomme 1948 *Beretningen vedrørende Grønlands styrelse No 2* 70–78
Leydhecker W (1973) *Glaukom Ein Handbuch* pp 281–293 Springer Berlin Heidelberg New York
Loh R C K (1968) The problem of glaucoma in Singapore *Singapore med J 9* 76–80
Lowe R F (1961) Angle closure glaucoma Acute and subacute attacks Clinical types *Trans ophthal Soc Aust ?1* 65–75
Lowe R F (1963) Comparative incidence of angle closure glaucoma among different national groups in Victoria Australia *Brit J Ophthal 47* 721–727
Lowe R F (1964) Primary angle closure glaucoma with capsular exfoliation of the lens *Brit J Ophthal 48* 492–494
Lowe R F (1965) Primary angle closure glaucoma A short history *Trans ophthal Soc Aust 24* 80–88
Lowe R F (1969) Causes of shallow chamber in primary angle closure glaucoma Ultrasonic biometry of normal and angle closure glaucoma eyes *Amer J Ophthal 67* 87–93
Lowe R F (1970a) Anterior lens displacement with age. *Brit J Ophthal 54* 117–121
Lowe R F (1970b) Aetiology of the anatomical basis for primary angle closure glaucoma *Brit J Ophthal 54* 161–169
Lowe R F (1972a) Primary angle closure glaucoma Inheritance and environment *Brit J Ophthal 56* 13–20
Lowe R F (1972b) Anterior lens curvature Comparisons between normal eyes and those with primary angle closure glaucoma *Brit J Ophthal 56* 409–413
Lowe R F (1973a) Primary angle closure glaucoma Geographic and racial variations *Trans ophthal Soc N Z ?5* 81–84
Lowe R F (1973b) Primary angle closure glaucoma A review 5 years after bilateral surgery *Brit J Ophthal 57* 457–463
Lowe R F (19 5) Primary angle closure glaucoma Biometry and the clinician In Etienne R and Paterson G D Eds *International Glaucoma Symposium Albi 1974* pp ?41–260 Diffusion Generale de Librairie Marseille.
Luntz M H (1973) Primary angle closure glaucoma in urbanized South African caucasoid and negroid communities *Brit J Ophthal 57* 445–456
Mann Ida (1966) *Culture race climate and eye disease* pp 539–540 C C Thomas Springfield
Mapstone R (1968) Mechanics of pupil block. *Brit J Ophthal 52* 19–25
McLenachan J & Loran D F C (1967) Angle closure glaucoma and inverse astigmatism *Brit J Ophthal 51* 441–443
Millodot M (1975) Do blue eyed people have more sensitive corneas than brown eyed people? *Nature (Lond) 255* 151–152
Morgan R W & Munro M (1973) Refractive problems in northern natives *Canad J Ophthal 8* 226–228
Morgan R W Speakman J S & Grimshaw S E (1975) Inuit myopia An environmentally induced epidemic ? *Canad med Ass 112* 575–577
Murchland J B & Edwards F M (1975) Anterior chamber depth of eyes of full blood aborigines at a reserve in South Australia *Aust J Ophthal 3* 5? ?8

Nakajima A Kimura T Kitamura K Uesugi M & Handa Y (1968) Studies on the heritability of some metric traits of the eye and the body *Jap J hum Genet 13* 20–39

Norman Hansen C M (1911) *Ophthalmologiske iagttagelser hos et arktisk folk Hospitalstidende 54* 85?

Norskov K (1968) Primary glaucoma as a cause of blindness *Acta ophthal (Kbh) 46* 853–859

Olurin O (1975) Anterior chamber depth of Nigerians Paper read at the *Fourth Congr Int Soc geograph Ophthal* Edinburgh

Ortlepp J (1966) Messungen des Hornhautdurchmessers und krummungsradius als Beitrag zur Klarung der speziellen Struktur des Glaukomauges *Albrecht v Graefes Arch klin exp Ophthal 169* 194–198

Paterson G (1961) Studies on siblings of patients with both angle closure and chronic simple glaucoma *Trans ophthal Soc U K 81* 561–572

Raeder J (1923) Untersuchungen uber die Lage und Dicke der Linse im menschlichen Auge bei physiologischen und pathologischen Zustanden nach einer neuen Methode gemessen II Die Lage der Linse bei glaukomatosen Zustanden *Albrecht v Graefes Arch Ophthal 112* 29–63

Rosengren B (1931) Studien uber die Tiefe der vorderen Augenkammer mit besonderer Hinsicht auf ihr Verhalten beim primaren Glaukom II Die Kammertiefe bei primaren Glaukom *Acta ophthal (Kbh) 9* 103–179

Rysa P & Sarvaranta J (1974a) Thermography of the eye during cold stress *Acta ophthal (Kbh) Suppl 123* 234–239

Rysa P & Sarvaranta J (1974b) Corneal temperature in man and rabbit *Acta ophthal (Kbh) 52* 810–816

Skeller E (1949) Øjensygdomme i Grønland *Ugeskr Læg 111* 5?9–532

Skeller E (1954) Anthropological and ophthalmological studies on the Angmagssalik Eskimos *Meddelelser om Grønland 10? (4)* 1–211

Smith C & Mendell N R (1974) Recurrence risks from family history and metric traits *Ann hum Genet 37* 275–286

Smith Priestley (1887) On the shallow anterior chamber of primary glaucoma *Ophthal Rev 6* 191–20?

Smith Priestley (1890) On the size of the cornea in relation to age sex refraction and primary glaucoma *Trans ophthal Soc U K 10* 68–80

Smith Priestley (1910 1911 1912) Glaucoma problems *Ophthal Rev 29* 289–296 3?3–365 *30* 33–44 97–107 161–173 *31* 1–8 65–75 129–138 193–203 288–296

Smith R (1958) The incidence of the primary glaucomas *Trans ophthal Soc U K 78* 215–259

Sorsby A Leary G A & Fraser G R (1966) Family studies on ocular refraction and its components *J med Genet 3* 269–273

Steegmann A T (1970) Cold adaptation and the human face *Amer J phys Anthrop 32* 243–250

Steegmann A T (1972) Cold response body form and craniofacial shape in two racial groups of Hawaii *Amer J phys Anthrop 37* 193–221

Steiger A (1907) Studien uber die erblichen Verhaltnisse der Hornhautkrummung *Z Augenheilk 17* 307–317

Storey J K & Phillips C I (1971) Ocular dimensions in angle closure glaucoma *Brit J physiol Opt ?6* 228–242

Sugar H S (1941) The mechanical factors in the etiology of acute glaucoma *Amer J Ophthal 24* 851–872

Suzuki Y & Kitazawa Y (1974) Primary glaucoma and the iris pattern *Acta Soc ophthal Jap 78* 1 8–185 (Excerpta med. (Amst) Sect XII (1975) 29 No 1031)
Tomlinson A & Leighton D A (1973) Ocular dimensions in the heredity of angle closure glaucoma *Brit J Ophthal 57* 475–486
Tornquist R (1953) Shallow anterior chamber in acute glaucoma A clinical and genetic study *Acta ophthal (Kbh) Suppl 39*
Tornquist R (1956) Chamber depth in primary acute glaucoma *Brit J Ophthal 40* 421–429
Tornquist R (1957) Corneal radius in primary acute glaucoma *Brit J Ophthal 41* 421–424
Tornquist R (1959) Peripheral chamber depth in shallow anterior chamber *Brit J Ophthal 43* 169–176
Westerlund E (1947) *Clinical and genetic studies on the primary glaucoma diseases* Busck Copenhagen
Wibaut F (1932) *Biologisch statistische Refraktionsuntersuchungen* p 85 Bergmann Munchen
Wyatt H (1973) Corneal disease in the Canadian north *Canad J Ophthal 8* 298–305
Wyatt H & Ghosh J (1970) Behavior of an iris model and the pupil block hypothesis *Brit J Ophthal 54* 177–185
Wyatt H Balisky L A & Singh O (1974) Acute glaucoma in Arctic Studies of the difference between the Eskimo and Indian peoples and of the effects of myopia in each group Paper read at the *Third int Symp on circumpolar Health* Yellowknife N W T Canada
Young F A Leary G A Baldwin W R West D C Box R A Harris E & Johnson C (1969) The transmission of refractive errors within Eskimo families *Amer J Optom 46* 676–685
Young F A & Leary G A (1971) Comparative oculometry of Caucasians Eskimos and chimpanzees In Bock J and Ossoinig K Eds *Ultrasonographia medica* Vol II pp 595–612 Wiener medizinischen Akademi
Young F A & Leary G A (1972) The inheritance of ocular components *Amer J Optom 49* 546–555
Young J D H & Finlay R D (1975) Primary spheroidal degeneration of the cornea in Labrador and northern Newfoundland *Amer J Ophthal 79* 129–134

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SUPPLEMENTUM 128

A K. K. K. LUNDSGAARD EDI COEPTA

Prematurity and the Eye

Ophthalmic 10-Year Follow-up of Children of Low and Normal Birth Weight

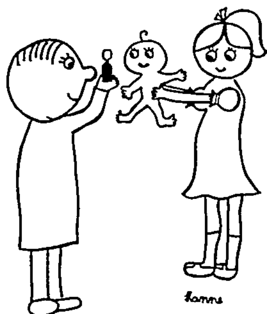
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Hans Fledelius

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Prematurity and the Eye

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København den 10 oktober 1975

Bent Sørensen
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CONTENTS

Introduction and approach 11

Chapter 1 General review of the literature on prematures 13
Factors of general importance to premature series 13
Birth weight limits Extent of neonatal service Social geographic and racial factors Ocular findings and CNS-damage
Summary and conclusions 17

Chapter 2 Present material 19
Basic material (The Copenhagen University Project 1959-61) 19
Previous ophthalmological studies
Ophthalmological material 21
The premature and the mature group Birth weight age and sex Gestational age Single-multiple pregnancy Relation to basic material Representativeness Comparability
Summary and conclusions 30

Chapter 3 Methods I 31
Standard programme of the ophthalmic examination 31
Statistical analysis of the results 32
Discussion 34
Summary and conclusions 34

Chapter 4 Methods II (Oculometry with ultrasound) 35
Methods of oculometry 35
Present ultrasonic technique 36
Sources of error discussion 41
On the total accuracy in ultrasound oculometry 45
Concluding remarks 45

Chapter 5 Refraction
Review of the literature 47
Refraction pattern during childhood
Refraction in prematures (Neonatally/ during preschool age/ during school age)

Method Present determination of refraction 52
Present results 53
Total premature and mature group 53
Refractive values Anisometropia Astigmatism
Supplementary analyses of children with myopia 61
Degree of myopia Correlation between birth weight and refractive value Time of onset of myopia Hereditary predisposition
The final refraction diagnoses 69
Discussion 69
Relation to previous studies Astgmatism Possible aetiological factors
Summary and conclusions 73

Chapter 6 Refractive components 75
Review of the literature 75
Differences in methods and materials The emmetropic adult eye Sex difference Co-variation of the optical components
Present results 79
Refractive components 79
Axial eye length chamber depth lens thickness and vitreous length Radius of corneal curvature
Correlation between refraction and refractive components 85
Refractive subgroups in the material 89
The main group around emmetropia Pre-school myopia Anisometropia
Discussion 93
Optical calculations in relation to oculometry
Special considerations for pre school myopia
Summary and conclusions 97

Chapter 7 Height and other somatic parameters 99
Patterns of growth 99
Present results 100
Height and age Percentile height Percentile height and maternal height Circumference of skull interpupillary distance ocular protrusion and corneal transverse diameter Correlation between the various growth parameters
Discussion 108
Influence of prematurity Permanent or temporary deficit in prematures Prematurity and ocular protrusion Association between growths parameters and refraction Social factors Aetiological considerations
Summary and Conclusions 111

Chapter 8 Visual acuity 113
Introduction and review of the literature 113
Physiological development of visual acuity
Abnormal visual acuities among children
Present findings 116
Binocular visual acuity Monocular visual acuity
Discussion 122
Summary and conclusions 125

Chapter 9 Binocularity 127
Introduction 127
Review of the literature 128
Prevalence of (1) heterotropia in the general population (2) hetero tropia among prematures and (3) prematurity in squint series
Heterotropia CNS-damage and prematurity Ratio between eso- and exodeviations
Definitions and methods used in the present study 135
Present results 138
Motor tests
Sensory tests
Some items further elucidating the binocular deviants
Concomitant/incomitant squint Constant/intermittent squint Small squint angles Correspondence Amblyopia Time of onset of squint Hereditary predisposition Refraction Anisometropia Aetiological considerations
Discussion 155
Summary and conclusions 157

Chapter 10 Ophthalmoscopy 159
Review of the literature 159
Ophthalmoscopy during the neonatal period RLF
RLF stage 0-I Summary of the literature
Present results 163
Major and minor retinal damage Other findings
Discussion 168
Summary and conclusions 170

Chapter 11 Lens 171
Review of the literature 171
Congenital cataract definitons and materials Cataract of prematurity Remnants of foetal vascular systems
Present findings 175
Discussion 177
Summary and conclusions 178

Chapter 12 Ocular malformations Additional ocular findings 181
Present findings 181
Discussion 183
Additional ocular findings 183
Summary and conclusions 184

Chapter 13 Multiple pregnancy 185
Present findings 185
Matched pairs Prematures of single and of multiple birth
Discussion 190
Summary and conclusions 191

Chapter 14 Ocular findings in relation to some obstetrical paediatric data 193
Factors concerning pregnancy 193
Social status Maternal proteinuria anaemia blood groups sensitization and smoking Single or multiple pregnancy
Factors concerning the child 194
Asphyxia Neonatal jaundice Oxygen therapy CNS damage (juding by early and present findings)
Summary and conclusions 198

Chapter 15 Closing remarks 199
Differences in ophthalmic status between premature and mature group 199
Visual disablement in the premature group 200
The trauma of prematurity 200
Practical consequences of the study 200

Summary 203

Summary in Danish 209

References 215

Subject Index 235

Appendix (41 case histories) 239

PREFACE

The present publication is based upon clinical studies performed in the University Eye Clinic Rigshospitalet Copenhagen from 1969 to 1972

My interest in the subject was aroused by Jens Edmund M D Consultant in the Eye Clinic who pointed out the importance of examining also ophthalmologically the children of low birth weight included in 'The University of Copenhagen Project 1959-61 This idea was ardently supported by Professor Holger Ehlers M D and Professor Preben Plum M D and a fellowship rendered it possible for me to embark upon the job The greatest measure of practical help I recived from Bengt Zachau Christiansen M D.. Without his enthusiasm and thorough knowledge of the basic paediatric material the ophthalmological project could not have been carried through From Professor Eilif Gregersen M.D I received valuable support during the planning phase as well as during the study period proper

To these people I am extremely grateful The same applies to Sigurd Ry Andersen M.D Head of the Institute of Eye Pathology University of Copenhagen who afforded me good working conditions during the final analysis of the clinical data During this phase I also had fruitful discussions with Viggo Dreyer M D

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The front page drawing is by my daughter Hanne aged 9 who suffered with the rest of the family while the study was in progress

Last but not least my thanks are due to the children and parents who so kindly participated in the study

Rungsted March 1976

Hans Fledelius

INTRODUCTION AND APPROACH

Infants of a low birth weight constitute a risk group having a high mortality and — among survivors — also a high morbidity Cerebral palsy is one of the most established entities but less severe clinical syndromes occur too Knobloch & Pasamanick (1959) thus emphasized a continuum of cerebral damage *increasing in severity* with decreasing birth weight As the most severe sublethal states they classified cerebral palsy epilepsy and pronounced mental deficiency as mild cases e g learning *and behavioural disorders A syndrome of minimal cerebral damage* in infancy has been used to describe such minor disturbances

For many years the paediatric aspects were all predominant the sporadic oph thalmological contributions dealt mostly with the occurrence of squint among children born prematurely After Terry s (1942) description of retrolental fibroplasia (RLF) and subsequent years explosive spread of this disease however the ophthal mologists became closely involved in the management of the premature infant Inter est was very naturally focussed on the violent retinal reaction which often involved blindness and which in many countries was to predominate the statistics on blindness in children After it was realized that the main cause of this disease was excessive oxygen therapy of premature newborns and appropriate precautions had been instituted the number of new cases abruptly dropped A tragic chapter on iatrogenic injuries appeared to have come to an end

Intensive research concerning this retinopathy of prematurity entailed other *clinical discoveries including a better general knowledge of the ophthalmological* status during the neonatal period For instance evidence of myopia of prema turity and of cataract of prematurity was adduced However the social conse quences of these conditions are *far less extensive than in the case of RLF which is* still the eye disease that doctors and laymen relate to premature infants — regrettably with good reason The hope that RLF would completely disappear was not fulfilled This syndrome is still among the most common causes of major visual impairment in children inhabiting civilized countries with highly developed hospital facilities

Developmentally the eye is a part of the central nervous system Biologically then all degrees of perinatal ocular injuries may be present concurrently with the continuum of cerebral damage However this is not apparent from the existing

ophthalmological literature which has very naturally been concentrated on the most disabling part of the morbidity spectrum It is the most injured fraction of the pre matures that keep up contact with the hospital environment and thus influences the impression of ocular sequelae to premature birth quantitatively as well as qualitati vely

It is considerably more difficult to find an answer to the questions *What has prematurity in fact cost a representative group of prematures from the ophthal mological point of view? How frequent are the really disabling ocular disorders and how frequent are the milder functional disturbances or minor damage?*

It was in order to elucidate these aspects that the present study was performed The method was to compare the ocular status in a group of children whose birth weight had been low (under 2000 g) with that in a group of children of the same age whose birth weight had been 3000-4000 g The children were investigated at the age around 10 years i e at a time when the growth and functional development of the eyes are believed to have been practically completed

By evaluating visual acuity refractive values and refraction components hetero tropia and binocular function ophthalmoscopic findings and lens changes etc it was endeavoured to *elucidate the influence of the prematurity trauma upon the subsequent development and function of the eyes*

CHAPTER 1

GENERAL REVIEW OF THE LITERATURE ON PREMATURES

A number of factors must be taken into consideration when assessing and comparing different series of prematures Experience paediatric as well as opthalmological is based upon studies with fairly different criteria and aims – The results of the pre sent investigation should be viewed in relation to existing knowledge within the field Accordingly a general discussion of some factors is needed before submitting the present material

Factors of General Importance to Premature Series

Birth Weight Limits

Birth may be considered a biological road accident on the *via naturalis* which leads from the intrauterine to the extrauterine world Every newborn infant has been exposed to a cranial injury of varying severity to a state of suffocation of varying length and is knocked about in a metabolic and circulatory sense (Lind 1969) This violent change in living conditions is not equally well tolerated by all infants Among the numerous individual perinatal parameters birth weight has proved of particular importance We can point out an optimal birth weight class of 3000 4000 g at which the risk of neonatal mortality is lowest (McKay 1969) At a lower birth weight in particular the risk increases and on an empirical basis a limit of 2500 g (Ylppo 1919 WHO 1948 50) has been selected in deciding whether the infant is to be considered full term or premature

But it is not enough that the premature infant pulls through the birth process Raiha (1962) said A premature infant is always at a disadvantage as it starts extrauterine life at a developmental stage which normally ought to run its course *in utero* The infant is immature and exhibits functional insufficiency The earlier the pregnancy is interrupted the greater the infant s congenital weakness" The congenital weakness or lacking maturity manifests itself in a high neonatal mortal ity and also in the increased incidence of permanent functional deficit

Experience from neonatal units has gradually shown that the accepted weight

limit of 2500 g is too high The majority of infants weighing between 2000 and 2500 g manage just as well as those who are by definition full term and need no special neonatal treatment Drillien (1964) among many others has advocated a limit of 2000 g as being more realistic Infants below this birth weight often need special care because of functional immaturity As a group they are characterized by a greater number of stillbirths a higher neonatal mortality and – among the sur vivors – more handicaps in life

For other reasons too the weight limit of 2500 g is inexpedient In the materials of Drillien (1964) and McKay (1969) 30 50% of the infants under 2500 g ('low birth weight) had been born at term i e after a gestational period of at least 37 weeks reversely a number of infants born after a gestational period shorter than 37 weeks (prematures) weigh more than 2500 g at birth It may be concluded in brief that the weight limit 2500 g is unsuitable for two reasons In part it is too high according to an estimate of the level of the actual risk limit, in part it results in far too many infants being defined as premature although they have not been born *before* term Lastly it pays no heed to racial differences in birth weight – This leads to the question whether other clinical signs of lacking maturity might replace birth weight as a criterion The answer is that in spite of all birth weight is the most accurately measurable and least subjective of all such parameters Thus the term 'low birth weight is logical more precise but the synonym prematurity has gained quite some footing in medical language all over the world

Indeed many authors have taken these factors into consideration selecting weight limits lower than the 2500 g especially when trying to analyse the risk to the lowest birth weight groups This risk will be completely submerged in collected analyses of groups of prematures comprising all infants weighing ⩽ 2500 g This may be illustrated by values calculated on the basis of Danish analyses of birth weight and survival of infants born during the year 1959 (Matthiessen et al 1967) In their material more than 75% of all surviving prematures belonged to the weight group 2001 2500 g and less than 5% weighed ⩽ 1500 g An example of the influence of this disproportion is Castren s (1955) oft-cited material of 480 prematures which – ophthalmologically – gives a fairly optimistic outlook on the subsequent fate of prematures The explanation is among others that more than 77% of the infants were in the most favourable weight group 2000 2500 g A birth weight below 1750 g was found in only 39 infants or 8% of the total series – This clearly illus trates the extremely decisive importance of birth weight limits in comparing materials

Extent of Neonatal Service

The marked disagreement between the published follow up studies on children with low birth weight Lubchenco (1968) commented as follows 'The progno is for normal development appears to have worsened during the past ten to fifteen years suggesting either a more accurate diagnosis of handicaps an improvement in mortali ty rate resulting in the survival of more infants with brain damage and other defects or changes in postnatal treatment adversely affecting the development of the small

premature infant Thus it would be wrong to view the prognosis of prematures merely on the basis of birth weight Robinson & Robinson (1965) stated Low birth weight has come to be seen as only one variable which is involved in a tangled web of etiology

Let us briefly look back 'Prematurology may be divided into four epochs the first of which may be called *survival of the fittest* Only the most viable infants survived as no special treatment was available It was believed that prematures developed on an equal footing with full term infants with the sole exception of the relatively few cases of severe brain damage (Ylppo 1919 Hess Mohr & Bartelme 1934 Beskow 1949)

Introduction of a *liberal oxygen therapy* for premature infants instituted the next epoch It had been realized that the alarming periods of apnoea and attacks of cyanosis are far less frequent when the inspired air is enriched with extra oxygen The oxygen is best administered in incubators which aim at *an environment corre sponding* as closely as possible to intrauterine life isolated from the surroundings and with a stable climate of suitable temperature and moisture These precautions marked a great advance resulting in a reduced neonatal mortality and fewer cases of hypoxic brain damage

This therapeutic gain however was at the expense of a common occurrence of blindness because of retrolental fibroplasia (RLF) (Terry 1942) Such cases occurred especially where neonatal service seemed most advanced Nevertheless a decade passed before the mystery was solved Not until then was it established that the administration of oxygen which had been thought devoid of risk was potentially toxic to the immature retinal vessels in premature infants -- This was the beginning of the epoch of *restrictive oxygen administration.* Now the oxygen content of the incubator was kept below a presumed risk limit of 40% However such a risk limit *proved illusory On the one hand* RLF *may occur at oxygen concentrations lower* than 40% On the other hand sticking to such a top limit will expose far too many infants to hypoxia during the neonatal period This applies especially to the more severe cases of the respiratory distress syndrome Silverman (1969) has called our present epoch the *determinative period* Oxygen is administered according to re quirement and the oxygen medication is best controlled by measurements of arterial oxygen tension in the newborn (Roberton et al 1968 Silverman 1969 Friis Hansen 1970 Kamper & Petersen 1973)

From the early 1950 s restrictive oxygen administration resulted in an abrupt fall in the incidence of RLF but even the most recent therapeutic advances and the most optimal oxygen control cannot prevent new cases from developing Regard to the severe hypoxic brain damage prevents the total discontinuation of oxygen therapy which would be desirable when considering only the retina

This brief review of neonatal therapeutic principles also hints at the difficulties in comparing materials from the different epochs The most striking example is naturally presented by materials from before and after the introduction of oxygen therapy It applies to Eames (1946) and Castren s (1955) materials for instance that they comprise almost exclusively infants to whom oxygen therapy had not been available Indeed these materials of prematures included no case of RLF Accord

ingly studies from that epoch may be called with some right, historical in relation to the conditions offered to premature infants born during the subsequent and more recent years – Moreover it is not possible to state any given years during which the named epochs have lasted The evolution has been gradual and besides there have been great geographical differences in time between the various countries and within each country

These considerations may be summed up as follows Every material of prematures reflects in principle primarily the possibilities of the premature infant for survival and optimal development but this must be viewed in relation to the conditions of living and the therapeutic possibilities prevailing at the time in the area concerned

Social Geographic and Racial Factors

Premature delivery occurs with increased frequency where there are poor conditions and social insecurity (Nørregaard 1953) which *per se* afford less favourable possibilities for rearing a child This can influence the child s performance in daily life at school and in the various test situations employed in neurology and psychology In analogy poorer cooperation and concentration might be expected in the various ophthalmological tests However the assessment of visual acuity and binocular function are such fairly simple procedures that the separate influence of social factors would appear to be minimal

Access to what is offered by public health service depends highly upon geographic factors traffic facilities payment for treatment etc Finally racial factors may manifest themselves int al in the birth weight level and if only for that reason major or minor fractions of newborn infants may be e g less than 2500 g Conceivably there may also be racial differences in resistance in the widest sense of that word

Association Between Ocular Findings and Damage to the Central Nervous System

The past few decades have witnessed the publication of a large number of papers dealing not only with severe cerebral damage among prematures but also with minor cerebral damage This is taken to mean minor intellectual impairment behavioural disturbances learning difficulties reading disabilities various kinds of apraxia stuttering psychological problems etc It is beyond doubt that such conditions are more common among surviving prematures than in the general population although the implications of these findings have been interpreted differently Let me refer to int al Beskow 1949 Alm 1953 Blegen 1953 Polani 1958 Knobloch & Pasamanick 1959 Douglas 1960 Lubchenco et al 1961 Takkunen et al 1963 Drillien 1964 Heimer et al 1964 Kantero et al 1965 Marstrander 1965, Robinson & Robinson 1965 Mendelson et al 1966 Wiener 1968 Illingworth 1970 Zachau-Christiansen 1972 – The neurological findings and mental status of prematures with RLF have been elucidated by Ingram & Kerr 1954 Norris et al 1957

Parmelee et al 1958 Williams 1958 Grant & Preston 1960 Bender 1964 and Genn & Silverman 1964

Retinal haemorrhages are common ophthalmoscopic findings during the first 24 hours of life These haemorrhages are believed to be caused by mechanical injury during delivery and usually subside in a few days without demonstrable late ocular sequelae (cf also Chapter 10) In analogy there must occur to a certain extent actual *cerebral* haemorrhages presumably as a rule small and situated in clinically silent zones However there is nothing to prevent such central – or more peripheral – haemorrhages from affecting the equilibrium of the ocular muscles at the crucial time before fixation and binocularity have properly developed In case of permanent sequelae the result is almost at all events the usual concomitant squint of child hood It is uncommon to encounter actual pareses of the eye muscles abnormal pupillary reactions visual field defects or other classical neuroophthalmological signs which usually accompany cerebral damage with an onset later in childhood

This supplies an indirect answer to the oft posed question whether "minor cerebral damage includes more specific ocular findings which directly reflect the extent of the damage It might be imagined for instance that the type of the squint – or the size of the squint angle – could directly disclose the type and severity of the original injury So far no such evidence has been adduced This question will be discussed in more detail in Chapter 9

On the other hand squint as such may be included as a neurological sign if only regard is paid particularly to the influence of hereditary factors It is well known that with increasing severity of cerebral palsy there will be an increasing frequency of squint as well as mental deficiency (Plum 1956) In their scoring system Heimer Cutler & Freedman (1964) included the presence of a squint as an item in fully assessing the neurological sequelae of prematurity

Summary and Conclusions

In a number of respects the available materials of prematures are inhomogeneous and a direct comparison of the results obtained from such materials may be diffi cult As factors of particular importance birth weight and the extent of neonatal service are pointed out

When the usual birth weight limit of 2500 g is kept up series of surviving pre matures are always numerically predominated by the infants of a birth weight in the vicinity of this limit Therefore the results are no reasonable reflection of the risk involved by a particularly low birth weight

Differences in neonatal service influence the mortality as well as morbidity and may accordingly give rise to marked differences in the results from study to study – This clearly stresses the obvious demand for suited control groups in clinical analyses

The association between ocular findings and damage to the central nervous system is briefly discussed According to the literature prematures more often ex hibit signs of major and minor cerebral dysfunction than do children born at term

A more detailed review of the literature to elucidate the association between ocular findings and prematurity will be given in the chapters dealing with the individual ophthalmological conditions and disease entities

CHAPTER 2

PRESENT MATERIAL

When instituting statistical investigations on the influence that a given factor has upon a variable quantity it is most correct to choose one s material with as little vari ation as possible in other factors which might exert an influence upon that quantity
(M Tscherning 1886)

The present ophthalmological study is based on an closely connected with a major prospective research project "The University Hospital of Copenhagen Project 1959-61 on the Significance of Gestation and Delivery for the Health and Development of the Child" Below some information is given on this *basic material* (a designation used throughout the chapters of the present study)

Basic Material

The prospective project has included int al two major clinical analyses (a) on con genital malformations (Villumsen 1970) and (b) on development during the first year of life with a special view to cerebral dysfunction (Zachau-Christiansen 1972) The interested reader is referred to the latter paper for details of the project itself which are given below merely in brief outline

The project was planned as a prospective study of about 10 000 pregnancies a number considered suitable if the material was to include also the more uncommon diseases and sub-groups The end result was 9 006 pregnancies resulting in 9 182 in fants and abortions over 250 g The pregnant patients were those consecutively admitted to the Maternity Departments of the University Hospital during the period 21 9 1959 to 21 12 1961 – The lower birth weight limit of 250 g corresponds to about one-half (20 weeks) of a normal gestational period In other studies a weight limit of 400 g has been used This discrepancy is of very little numerical importance Only ¼% of the 9 006 pregnancies resulted in foetuses in the weight group 251-400 g (25 in all with 24 stillbirths)

Of the 9 182 neonates 96 2% were of single and 3 8% of multiple pregnancies there being 170 sets of twins and three sets of triplets All the triplets survived the neonatal period (the first 4 weeks of life) 131 A twins and 122 B twins survived the neonatal period

By *birth weight and survival* the material was divided into

I	'Matures' (of a birth weight exceeding 2500 g) who survived the first 28 days	7,342
II	'Prematures (of a birth weight $\leqslant$ 2500 g) who survived the first 28 days	1 083
III	'Mature stillbirths	76
IV	'Premature stillbirths	286
V	Matures who died within the first 28 days of life	46
VI	'Prematures who died within the first 28 days of life	349

The distinction between matures and prematures was according to tradition based only upon the *birth weight limit of 2500 g* without paying regard to the gesta tional period and the clinical estimate of the infant s maturity

Out of the total 9 182 neonates 18 7% were premature Out of the 8 425 who survived the neonatal period 12 9% were premature Of the stillbirths and neonatal deaths (757 in all) 83 9% were premature

During the period 1959-61 the two Maternity Units admitted patients according to the following rules

(1) Pregnant patients with a history of pregnancy complications

(2) Pregnant patients with prospects of complicated delivery – including those with a history of previous obstetrical complications including abortions stillbirths or infants with birth damage (pregnancy wastage)

(3) Pregnant patients living under social conditions at which delivery at home must be considered inadvisable Of this group single mothers made up the great majority

Thus compared with the general Danish population the material is a heavy one from an obstetrical as well as social point of view This may be briefly illustrated by the following items

(a) During the period 1959-61 neonatal mortality in Denmark was 16.3 in 1000 live born and the number of stillbirths 13 2 in 1000 births (Matthiessen et al 1967) These values were almost trebled in the project material viz 44 8 neonatal deaths and 39 9 stillbirths respectively and this is in spite of the fact that the infants of the project enjoyed an obstetrical paediatric service optimal for that time

(b) The proportion of prematures was higher than the 5 7% in the general popu lation This may also be illustrated by calculations based on Danish statistics of birth weight grouping and mortality for the period in question (Matthiessen et al 1967) 25 30 000 Danish live born children would normally be required to obtain the number of surviving prematures of a birth weight under 2000 g that actually occurred among the less than 9 000 live born infants of the project material

(c) It is more difficult to specify the social skewness of the material especially in the absence of a suited Danish reference material of parents with an adequate

social classification Instead Zachau-Christiansen (1972) compared the basic material with the social distribution in an urban area in England and found no major discrepancies

Within the project there were 30% illegitimate births – as compared with 7 8% in the general population during that period Previously, illegitimate birth was almost synonymous with a low social status but by now the social implications have faded In point of fact these mothers were predominantly young healthy women with uncomplicated deliveries that consequently did not weigh on the material on the contrary they raised the average from an obstetrical paediatric point of view (Zachau Christiansen 1972) Incidentally severe indigence is rare in Denmark where all pregnant women at that time too had access to free pregnancy examinations the necessary obstetrical service and support also after delivery

Previous Ophthalmological Studies in the Basic Material

Ophthalmological studies have been merely sporadic At the institution of the project the University Eye Clinic was unable to place the needed capacity at free disposal and only a negligible part of the infants were assessed by ophthalmologists A total of 241 prematures of a birth weight not stated and 249 mature infants most of whom had been instrumentally delivered Retinal haemorrhages were found in 4% and 6% of the prematures and matures respectively and "cloudy media" in 23% and 2% respectively It is not accurately stated on which day of life the examinations were carried out and later there has been no systematic ophthalmological follow-up

Accordingly the evaluation of the ocular status rested mainly with the three paediatricians who assessed the infants total status on the 1st and 5th days of life and again around their 1 year birthday *Subconjunctival haemorrhages* were observed somewhat more often in mature infants (4 7% as compared with 0 6% of the pre matures) but no other differences were noted in the neonatal period. At the 1 year follow-up un-coordinated gaze was found in 4.3% of the mature and in 8 9% of the premature babies It has been explained (Zachau-Christiansen 1972 personal communication) that the term "un-coordinated gaze refers to the immediate impression of deviating ocular axes (squint)

On the basis of the available data it may be deduced (a) that ophthalmoscopy on premature infants often disclosed cloudy media during the first days of life and *(b) that at 1 year follow up there seemed to be twice as many "squinters"* among premature as among mature babies – It is apparent indirectly that as far as the eyes are concerned there is no basis for a longitudinal study in the sense recorded ocular changes between birth and the age of 10 years

Ophthalmological Material

The present ophthalmological study comprised two groups of children invited to attend around the age of 10 years *These children were selected from the basic ma*

terial according to birth weight criteria Below, these two groups will be called the premature group and the mature group

The Premature Group (302 Children)

This group had been planned to comprise all surviving children whose *birth weight had been less than 2000 g* To these were added 17 children of a birth weight ≥ 2000 g from multiple pregnancies who had a surviving co twin or co triplet in the < 2000 g group

The total group comprised 336 children 84 of whom were of multiple preg nancies (including the 17 of a higher birth weight) The lowest birth weight in the group was 800 g

Out of the 336 children I examined 302 (90%) who are included in the following analyses 272 attended at the University Clinic where investigative facilities were optimal 30 children were visited in their homes where they were examined of necessity in a somewhat reduced investigative programme

The distribution on the various birth weight classes may be seen from Table 2 1 As is evident from the recruiting of the material all the births had taken place in Copenhagen At the time of follow up only a small number of the children were living outside the Copenhagen area

Table 2 1 *Distribution of birth weights in the premature group*

Birth weight groups	Number of children available for study according to the records of the *basic* material	Number of children actually examined in the present study
Less than 1000 g	6	5
1001 1250 g	21	21
1251-1500 g	65	64
1501 1750 g	105	93
1751 1950 g	122	102
≧ 2000 g (multiple birth - see text)	17	17
Total premature group	336	302

In the case of the 34 prematures who were not examined ophthalmologically information was obtained from the school health service for 21 Two cases of heterotropia had been diagnosed one of them with amblyopia In all the remaining eyes the visual acuity was better than 6/9 For one of the four emigrated children ophthalmological information was obtained from the new abode This was a girl whose birth weight had been 950 g with early myopia squint and unilateral amblyopia

One child who ought to have been included in the premature group was not brought to my knowledge until *after* the study had been completed The invitation to attend for an ophthalmological examination had failed because for social reasons this child had been struck off the invitation list to the paediatric follow up examinations Below this child will be excluded from all tables and analyses but will be reported separately in case 41 (cf Appendix) because of the severe general (mental deficiency) and ocular findings (cataract severe impairment of vision heterotropia and nystagmus)

The Mature Group (237 Children)

As a control group 320 of the full term infants were selected from the material randomly but on the following conditions

Table 2 2 *Mean birth weight and mean age* (when examined ophthalmologically) of children of the premature and mature group (top) and divided by sex (bottom) Standard deviations in parentheses

		Birth weight in g Mean values ± SD		Age in years when examined Mean values ± SD	
Premature group	n = 302	1663	(± 283)	10.26	(± 0 94)
Mature group	n = 237	3462	(± 243)	10 28	(± 0 93)
Premature boys	n = 150	1697	(± 291)	10 36	(± 0 90)
Premature girls	n= 152	1630	(± 271)	10 18	(± 0 98)
Mature boys	n = 113	3500	(± 240)	10 29	(± 0 95)
Mature girls	n = 124	3427	(± 243)	10.27	(± 0 92)

(a) 'optimal birth weight – between 3000 and 4000 g
(b) dates of birth scattered evenly over the period from the institution to the end of the project
(c) births also evenly distributed on the four quarters of the year
(d) present domicile within Copenhagen and environments – to facilitate attendance

Out of the 320 children I examined 237 (74%) in the University Eye Clinic These 237 children make up the mature group in the following analyses The parents of 78 children did not respond to several written requests and those of five children definitely refused to participate

Among the 237 children examined there was no case of multiple birth

Birth Weight Age and Sex in the Two Groups

Table 2 1 presents for the premature group the distribution of birth weights on different weight classes

Table 2 2 sets out (a) the mean birth weight for the groups of the material (b) the children s mean age at the time of the ophthalmological examination and lastly (c) the sex ratio in the two groups

At ophthalmoligical follow up examination the age distribution was as shown in Fig 2 1

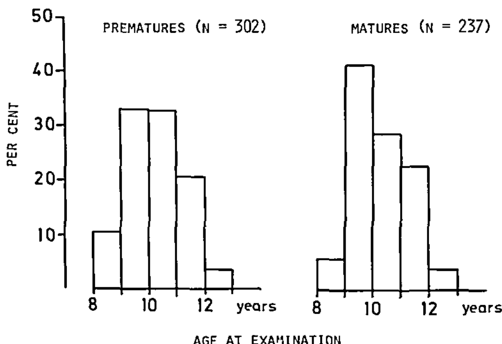


Figure 2 1 *Age distribution at examination*

Table 2.3 gives the gestational age of that part of the children (about 80%) in whom it was possible to make a satisfactory estimate in this respect About 95% of the

Table 2 3 *Gestational ages* at birth of the children belonging to the premature and mature group
Information available for 235 out of 302 premature infants and for 197 out of 237 mature infants
Distribution of percentage frequencies

		Premature group n = 235	Mature group n = 197
Gestational age in weeks	≧ 42 weeks	1 3%	10 1%
	41 38	10 6%	84 3%
	37-36	17 5%	4 6%
	35 34	15 7%	1 0%
	33 32	20 4%	
	31 30	21 3%	
	≦ 29 weeks	13 2%	

Table 2 4 *Gestational age* at birth (in weeks) *in different birth weight groups* of the material
Mean values and standard deviations

	Birth weight g	Number of children with information available	Mean gestational age (in weeks) ± SD	
Prematures	≦ 1250	23	30 6	± 3 2
	1251 1500	49	32 0	± 3 1
	1501 1750	69	33 4	± 3 5
	1751 1950	80	34 5	± 3 2
	≧ 2000 g (mult birth)	14	36 1	± 3 7
Matures	3050 3950	197	40 2	± 1 5

children in the mature group had been full term in the strict sense of the word having a gestational period ≥ 38 weeks In the case of the prematures the greater part had had truly premature birth In more than half the cases the estimated gestational age had been 33 weeks or less, 11 9% however had been born around term In this material no further analyses were done on the problem small for date

Table 2 4 demonstrates the mean gestational ages in the various birth weight groups As might be expected the shortest gestational periods were often associated with the lowest birth weights The standard deviations reflect the dispersion among the prematures The mature group, on the other hand was stable around the expected gestational period of 40 weeks

Single Multiple Pregnancy

All 237 children of the mature group were the product of single pregnancy

Of the 302 children in the premature group 81 were of multiple pregnancies viz 29 intact sets of twins with both A and B surviving 7 surviving A twins and 10 surviving B twins plus two intact sets of triplets viz surviving A B and C triplets

In seven of the 29 intact twin sets the children were of different sex and thus definitely dizygotic The remaining 22 intact sets were of the same sex Some of them were unmistakably monozygotic but an attempt at confirming or elucidating this further by blood and tissue specimens etc had rarely been made One set of surviving triplets consisted of three boys the other of one girl and two boys

The group of 81 children of multiple pregnancies also included the 17 of a birth weight ≥ 2000 g who were included in the study because a surviving co twin or at least one surviving co triplet was comprised by the study due to a birth weight < 2000 g These 17 children raised the mean birth weight up to 1767 g in the group of multiple births The 221 children of single pregnancies had been of a birth weight averaging 1625 g

The influence of multiple pregnancy will be further discussed in Chapter 13

Relation to Basic Material Representativeness

The Premature Group

By perusal of data from the basic material as already mentioned 336 children whose birth weight had been under 2000 g were found to be suitable candidates for the premature group of the ophthalmological study However this number does not quite agree with Zachau-Christiansen s (1972) tabulation of the number of surviving prematures According to his tables the prematures who survived the neonatal period were grouped by birth weight as follows 5 of a birth weight ≤ 1000 g 91 in the weight group 1001 1500 g and 303 in the group 1501 2000 g This makes 399 infants since the last group of 2001 2500 g is of no interest in the present context

This numerical difference (336 against 399) is primarily explained by the fact

that infants of a birth weight 2000 g are included in Zachau-Christiansen s but not in my material A manual search of the case notes revealed 46 infants of this birth weight Another 6 infants weighing less than 2000 g are known to have died within the first year of life *after* the neonatal period was over (Zachau-Christiansen 1972) whereas later deaths if any have not been recorded This reduces the real numerical discrepancy between the two materials to 11 infants one of whom was mentioned on p 23 Thus only 10 children were "lost to science" For coding reasons it was not possible to single out these 10 children by computer from the data of the basic material

The present premature group having a birth weight of less than 2000 g is considered *representative* of surviving prematures of the named low birth weight Such a group is always derived predominantly from hospital deliveries

The Mature Group

Two-thirds of the mature infants of the *basic material* were in the optimal birth weight class between 3000 and 4000 g from which the ophthalmological *control group* was recruited 26% had a birth weight of 2501 3000 g and from a prognostic point of view this group may be considered broadly speaking just as optimal A birth weight over 4000 g on the other hand entails a greater risk, but only 7.3% of the mature infants belonged to this high weight group Thus the ophthalmological control group (birth weight 3000 4000 g) must be considered on the whole less heavy than the total group of mature infants It is not possible to demonstrate the importance of this discrepancy and it is equally impossible to establish to what extent this group of infants born in hospital differs from mature infants in the general population as such – In other words the representativeness of the mature group is subject to discussion but I felt that such more hypothetical regards had to yield to the demands for *comparability* of the groups This will be elucidated below in eight items

Comparability of the Groups

The two groups of the ophthalmological material comply primarily with the fundamental demands on comparability identical time and place

(a) All the infants were from Maternity Units A and B of the University Hospital Copenhagen from the period 1959-61 This secures the same external environment and uniform general principles of treatment At that time a special neonatal unit had not yet been established

(b) Pregnancy factors had been uniformly elucidated by interviews with the mothers before or at the termination of pregnancy All the interviews were according to a questionnaire and conducted by the same doctor (Villumsen 1970)

(c) Perinatal data and neonatal symptoms were uniformly assessed This assessment too was according to a list and carried out by three paediatricians – The same

applied to the 1 year examination and the data collected concerning the development and morbidity during the first years of life (A number of the data mentioned under (b) and (c) will be discussed in more detail with regard to the children of the present ophthalmological material in Chapter 14)

(d) The children were of approximately the same age and school level at the time of the ophthalmological evaluation which was carried out in the University Eye Clinic by the same ophthalmologist according to a fixed study programme

(e) At the age concerned around 10 years ocular functions and dimensions are considered almost fully developed, in particular there is no reason to expect purely *age-conditioned* differences in ocular status neither *within* nor *between* the groups

Accordingly differences in ocular findings between the two groups ought to be attributable to the birth weight the only criterion of distinguishing the two groups However erroneous conclusions will result if there are differences between the two groups in the incidence of other traumas than the low birth weight The influence of heredity and environmental conditions may load the groups differently and affect the final results of the analysis A few such factors will be briefly discussed

(f) *Heredity* As a rule data supplied concerning heredity carry great inaccuracy int al because people on the whole do not know the exact meaning of the ophthal

Table 2 5 *Hereditary predisposition* to some eye diseases and ocular states as estimated from information given by parents in children of the premature group (left) and mature group (right) Frequencies (in per cent) of children with positive family histories i e one or more cases among the next of kin

	Prematures information available for 293 (of 302)	Matures information available for all 237
Early cataract (congenital juvenile or early adult)	0 3%	3 0%
Early glaucoma (congenital juvenile or early adult)	1 3%	0 4%
Congenital eye defects	0	0 4%
Squint	27 3%	21 1%
Defective colour vision	10 0%	11 0%
Myopia	20 1%	21 9%
Major degrees of hypermetropia astigmatism or anisometropia	7 5%	6 3%

mological terms The most reliable information is probably a positive report on squint in relatives However mild squint may be overlooked traumatic and other secondary forms of squint may be included branches of the family may be unknown to the interviewed person there may be cases of adoption or doubt about paternity etc There fore the values given in Table 2 5 should be assessed with caution even though it includes only data believed to be reliable As "reliable" I took conditions in the interviewed persons and their next-of kin which could be verified in examinations by myself or by ophthalmological colleagues Next-of kin is taken to mean – in a somewhat wide sense – siblings parents grandparents and parents siblings All persons who accompanied the children at the examination were questioned uniformly on this item It must be assumed that the inaccuracy attaching to the data has been the same in both main groups

According to Table 2 5 differences in heredity between the two groups can hardly have been particularly marked The relative preponderance of the prematures in the tendency to squint is not significant at the 0 05 level when assessed on the basis of the percentages listed However the latter represent only the presence of a predisposition not its massiveness The trend was towards a relatively *more* common occurrence of squint among the prematures next-of kin.

The predisposition to myopia and squint appeared equally distributed on both sexes

(g) The question of *racial factors* links up to some extent with heredity In this respect the Danish population has been stable and settled without major admixture through immigration The children of the ophthalmological material were almost exclusively of the Scandinavian/Northern European type, and racial differences can be excluded

Table 2 6 *Marital status of mother during pregnancy*
Information available for all infants except six in the premature group
Frequencies in per cent

		Premature group n = 296	Mature group n = 236
Mother	single unmarried	21 6%	21 1%
"Single	divorced separated widow	8 8%	5.5%
Married	before conception or during pregnancy	69 6%	73 3%

Table 2 7 *Social status of breadwinner at infant s first birthday* Information available about 262 prematures and 218 matures
Frequencies in per cent

	Premature group n = 262	Mature group n = 218
Social classes I + II	8 4%	14 7%
Social class III	55 3%	48 6%
Social classes IV + V	36 3%	36 7%

(h) Finally brief mention will be made of *social factors* (cf also Chapter 14) assessed on the basis of Zachau-Christiansen s (1972) perinatal data They included partly the mother s marital status (Table 2 6) and partly a social classification according to a British model (Table 2 7) Social groups I II comprise business and professional people and civil servants group III skilled workmen or clerks and business men on a small scale group IV semiskilled workmen or clerks and group V labourers

Tables 2 6 and 2 7 show no major social inequalities between the two main groups Rather more than one fifth of the mothers were unmarried at delivery and rather more than one third of the children were of the so-called lower social strata

Summary and Conclusions

The present material is described It consists of a premature group of a birth weight under 2000 g (n = 302) and a mature control group of a birth weight between 3000 and 4000 g (n = 237) At the time of the ophthalmological examination the children were around 10 years of age

The two main groups differ by virtue of their selection only in birth weight Both are derived from a major Danish prospective obstetrical paediatric research project The Copenhagen University Hospital Investigation 1959-61 on the Significance of Pregnancy and Delivery for the Health and Development of the Infant The main items of the project are outlined

From this study good and uniform data were obtained concerning perinatal factors and the first year of life – According to an analysis of such early factors the comparability of the two ophthalmological groups must be considered really good

Through a high tracing rate it was possible to obtain a representative picture of both groups This constitutes a decisive difference in relation to a number of previous materials Such series seem weighted on the whole by the children whose parents were most willing to cooperate and often this is tantamount to the divergent and directly abnormal cases

CHAPTER 3

METHODS I

Standard Programme of the Ophthalmological Examination

The examination and assessment of the 539 children in the ophthalmological ma terial were done by myself in all cases but with unhindered access to advice from my *orthoptic and ophthalmological colleagues of the University Eye Clinic*

Most of the children – 509 – were examined under optimal conditions in the Eye Clinic In the course of one consultation all were subjected to a fixed examin ation programme For practical reasons this programme had to be somewhat reduced in the case of the remaining 30 children (all premature) who were visited and examined in their homes

The Standard *Programme may* be Outlined as Follows

(a) *History*

(1) Data concerning the *familial occurrence* of various eye diseases congenital malformations early cataract or glaucoma squint colour vision defects myopia and myopic complications other major refraction anomalies

(2) *Personal history* viz data concerning infections ocular injuries previous ophthalmological examinations and treatment reading disabilities school com *plaints* etc

(b) Examination of the *ocular surroundings* inspection and palpation af the orbits eyelids etc

(c) *Ocular function*

(1) *Ocular movements* also including determination of the near points of con vergence and accommodation (NPC and NPA)

(2) Determination of the optimal *visual acuity* – binocular and monocular – with Snellen s chart at 6 m distance

(3) *Binocular function* Cover tests with prism rod measurements of deviations

from orthophoria, Maddox rod at 6 metres and Maddox wing the Worth four dot test at 6 metres and at near (35 cm), Titmus stereopsis test and evaluation in syn optophore

(4) *Colour sense* was investigated with Ishihara s plates

(d) *Slit lamp examination* of the eyelids conjunctiva cornea anterior chamber, iris lens and vitreous body

(e) *Ophthalmoscopy in mydriasis*

(f) A set of *oculometric measurements* comprising

(1) Assessment of ocular *refraction under cycloplegia by retionscopy* if possible also confirmed subjectively

(2) *Javal-Schiøtz keratometry* (Haag-Streit) determining the central corneal radius of curvature (vertex power) the degree of corneal astigmatism and the main meridians

(3) *Determination of axial length* under cycloplegia with ultrasound (Time Amplitude Ultrasonography A mode) i e *measurement of the axial chamber depth* lens thickness and vitreous length Further details of the technique will be given in Chapter 4

(g) A number of *other somatic measurements*

(1) Body height measured in cm the child in the erect position

(2) *Circumference of skull* measured in cm to the nearest half at the level of the external occipital protuberance posteriorly and of the glabella anteriorly

(3) *Interpupillary distance* measured in mm the child fixing a punctate light source at 6 m distance

(4) *Transverse diameter of cornea* measured with a Zeiss meter to the nearest quarter mm

(5) *Exophthalmometry* stated as the prominence in mm of the corneal vertex in relation to the lateral orbital margin The measurements were performed with a modified Luedde rod and supplemented with Hertel measurements only in the event of a side difference or other doubt

In the case of the 30 children examined in their homes keratometry, syn optophore and slit lamp examination as well as the ultrasonic measurements had to be omitted It applies also to a few other examinations that results had to be excluded for instance in some cases where a given test was not included as a fixed link in the programme until after the start of the project Accordingly the following analyses of the results often comprise somewhat fewer children than the total number in the two groups (302 prematures and 237 matures)

Statistical Analysis of the Results

Various statistical tests were used in analysing the results Most were non parametric tests as the analysed data seldom fulfilled the criteria of parametric significance

testing (as clearly described by e g Siegel 1956) Parametric tests were used especially for the oculometric parameters (Chapter 6) measured in interval scale and showing an approximated normal distribution

The data were transferred to punch cards (160 columns) and a number of calculations (mean values standard deviations correlation and regression coefficients medians and fractiles etc) were carried out by the aid of standard computer programmes Various statistical tests were also done by machine (Mann Whitney Kruskal Wallis) but in most cases the statistical evaluations were done manually after additions and tabulation of the data which were felt relevant according to the present approach As statistical manuals mainly Siegel s (1956) Therkelsen s (1968) and Andersen s (1971) were used supplemented by the tabulations in the 6th edition of Documenta Geigy Scientific Tables (1962)

The statistical tests will be mentioned wherever they were employed Significant values are given by $p < 0\ 05$ or $p < 0\ 01$ At levels $> 0\ 05$ the results are designated as not significant

Otherwise the conditions of the significance testing were on the whole kept as conservative as possible Two items should be briefly mentioned in this connection (1) Two way analyses were used (2) As a rule the statistical calculations were based upon number of *individuals* not of *eyes*

As regards the former it should be borne in mind that in two way testing on the basis of the null hypothesis the importance of differences between groups are assessed without paying regard to whether the difference is expected into one direction or the other In a number of the present approaches however it seemed not unreasonable to set up an alternative "signed hypothesis For instance the prematures are often expected to give a poorer (not merely divergent) performance than the mature group

The other factor – number of eyes or number of individuals – was most recently discussed by Ederer (1973) His analysis may be interpreted as an attack on the abuse of using *number of eyes* (rather than individuals) in some clinical opthalmological analyses This affords a sometimes unjustified duplication of the size of the material – and thus also higher (and more "becoming) X^2 values However the factual information does not correspond to *number of eyes* if the ocular parameters considered show a marked right left correlation

Still this has its special facettes in analyses of prematures For instance it is known that retrolental fibroplasia (RLF) may affect the two eyes to a different degree (Zacharias et al 1962) and this influences possibly abolishes the usual right left correlation In selected instances therefore it is justified to base calculations on the number of eyes rather than of individuals In the majority of the approaches under study however the number of persons is the most reasonable basis when analysing the various forms of ocular damage

The conservative conditions used here lead to a relatively smaller number of significant results i e less risk of statistical type I errors

Discussion

The examination programme was a compromise between what was theoretically desirable and what was practicable *for the purpose of obtaining uniform and reliable data for the total material*

In practice the programme was fixed with a view to *how* much the children could stand and for *how* long without losing interest and cooperation It was neces sary therefore to fix some order of priority weighing the extra information obtain able by a test against the time that it would take and – especially – against the dis comfort or the risk that it might involve For instance ophthalmological examination under anaesthesia would have been desirable in several children but was never forced upon them

Among the more arduous procedures only ultrasonography was performed whenever possible, as it was desired to correlate the refraction values with the various refraction components Ultrasonic measurement was always the last item of the programme At that time the necessary confidence had been established, and a possibly negative reaction would not influence other results A large number of the children gave their willing cooperation to the extent which is needed to obtain appli cable results As might be expected other children could not be persuaded especially those who had reacted violently already to the instillation for cycloplegia

In practice the programme could be completed within an hour and a half The only sequel was cycloplegia for a few hours

As already mentioned the ultrasonic technique will be described in more detail in the next chapter Other methods will be discussed to some extent in the relevant chapters

Summary and Conclusions

All 539 children were examined by the same examiner

The examination programme is outlined It was composed with a view to the practical regard as to what cooperation could be expected from children aged about 10 years in the course of one consultation (1 ½ hours)

To elucidate refraction components ultrasonic oculometry was carried through in the majority of children in the ophthalmological material while other arduous procedures were omitted

The methods of statistical calculation are described

CHAPTER 4

METHODS II

Ultrasonic Oculometry

Axial ultrasound oculometry is a rapid and reliable method of measuring eye dimen sions It is devoid of risk and has largely replaced earlier methods of measurement Since however the latter have been used in a number of important refraction studies they will be briefly recapitulated

Measurements on cadaver eyes afforded the first important information about ocular dimensions and their relation to refraction Schnabel & Herrnheiser (1895), for instance established that myopic eyes usually have a longer axis than emmetropic and hypermetropic eyes although some overlapping exists

Optical measurements Assessment of axial eye length *in vivo* was rendered pos sible by calculations based upon optical measurements (viz the size of Purkinje s mirror images on the refractive surfaces of the eye (Helmholtz 1896 Tscherning 1898) keratometry and determination of refraction value) Among the classical oculometric studies there is reason to mention Lindstedt (1916) Wibaut (1926 1932) Tron (1929 1934) Rosengren (1930) Stenstrom (1946) and Tornquist (1953) Goldmann (1940 1961) based his optical method upon slit lamp photo-graphy In recent times too Sorsby and associates (1957 1961 1970) have preferred the optic methods Sorsby reported a cumulative effect of inherent error of ± 0.3% on the instrumental readings He also pointed out that considerable errors will result even from small individual divergences from the standard refraction indices used for calculation

X-ray method Measurement of the ocular axis was rendered possible by the aid of quite a different physical principle viz X rays (Rushton 1938) This could elimi nate the uncertainty concerning the numerous premises underlying the optical calculations Though theoretically so ideal this method proved unhandy Only Stenstrom (1946) has used the principle on a major scale

Ultrasonic methods were soon developed after the publication of the first ocular axial echogram (Mundt & Hughes 1956) From the early 1960 s the first major materials of ultrasonic eye measurements began to appear (Yamamoto et al 1960 Franken 1961 and 1962 Jansson 1961-63 Gernet et al since 1963) A bibliography

of the abundant ophthalmological literature on ultrasonics up to 1968 may be found in Ophthalmic Ultrasound' (Editors Gitter Keeney, Sarin & Meyer C V Mosby, St Louis 1969)

The methods described for determining axial lengths in living eyes have shown reasonable conformity (Sorsby 1967, Jansson 1963 Kimura et al 1969) Optical methods are still used by some ultrasound workers for measuring anterior chamber depth and combined with ultrasonic measurements of the posterior segment of the eye The X ray method seems to have been entirely abandoned Owing to the great demands on cooperation it is difficult to operate and besides the patient is exposed to some radiation risk

At present the most common method is the rapid A mode of ultrasonic measurement of the eyes a procedure which is being further developed especially by using higher ultrasonic frequencies (meaning better resolution) and more accurate electronic time marking

Present Ultrasonic Technique

The axial ultrasonic measurements were by the same technique and equipment as in previous publications (Fledelius 1970 1971) In principle it is based on Jansson s (1963) Its details will be described and discussed below

Equipment and Calculations

The *ultrasonic equipment* Kretztechnik 7000, permits time amplitude ultrasono graphy with A mode echograms

The *probe* was the Ultrasonolux transducer developed by Buschmann (1963) which has a frequency of 12 mHz a crystal diameter of 2 5 mm and a slightly fo cused sound beam

Between the transducer and the eye a *contact glass* was interposed Its lumen was filled with 2% methyl cellulose (Methocel) in order to obtain from the anterior surface of the cornea a well defined echo quite separate from the initial echo of the transducer (Fig 4 1)

Measurement of ocular dimensions was performed by means of a built in *poten tiometer* which moves a threshold on the basic line of the oscilloscope screen from echo to echo This made it possible to state in arbitrary potentiometric units the distance between the sound reflecting interfaces in the ocular axis (Fig 4 2)

Calibration was to ultrasound passage through distilled water at room tempera ture by means of a Kretz *interferometer* For every 2 mm change of the water distance and the associated shift of echo the relevant potentiometric scale value was read Within the range of measurement employed in practice there was satisfac tory linearity on the screen (Fig 4.3) Only negligible errors were introduced when the *mean* water distance per potentiometric unit was used as a basis of further calculations

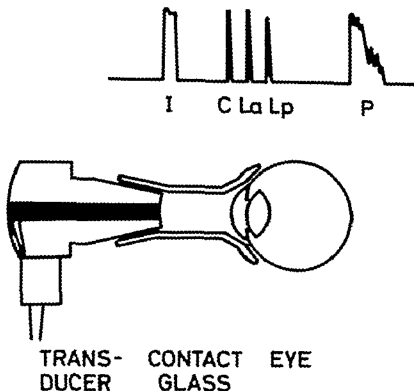


Figure 4 1 Schematic drawing of the *ultrasound measuring conditions* with transducer contact class and eye (bottom) and the axial echogram (top) I = initial echo C = echo from anterior corneal surface L_a and L_p = anterior and posterior lens echoes P = posterior wall echo from the vitreo-retinal interface

Conversion into the actual ocular distances was based upon the mean velocities published by Jansson (1963) of ultrasound propagation in the anterior chamber and vitreous body (1532 m/sec) and in the lens (1641 m/sec)

Sound velocity v in the reference medium – distilled water – was stated in *Willard s (1947) formula*

$$v = 1557 - 0\ 0245\ (74 - t)^2 \text{ m/sec}$$

where t is the temperature in centigrade

In a random calibration (Fledelius 1970) 100 potentiometric units corresponded to 7 346 mm distilled water at 20 C The sound velocity in the water could be fixed at 1486 m/sec Thereafter chamber depths and vitreous lengths could be calculated (in mm) by multiplying the corresponding water distances (in potentiometric units) with $0\ 07346 \times \frac{1532}{1486}$ and lens thicknesses in the same way with $0\ 07346 \times \frac{1641}{1486}$ No other correction factors were used (cf also the discussion p 41)

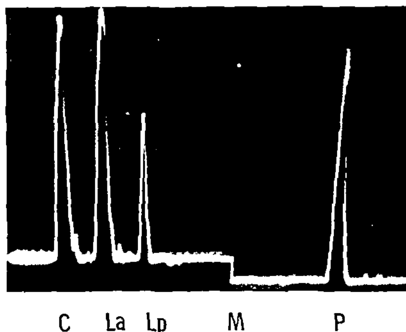


Figure 4 2 Polaroid photo of an *axial ocular echogram*, M designates the measuring threshold of the potentiometer (see also text)

The Method in Practice

The ultrasonic apparatus was put on at least 15 minutes before measurement to guard as far as possible against varying degrees of heating from measurement to measurement

The child was examined supine (Fig 4 4) the free eye directed at a green fix ation light in the ceiling above his head This kept him still and relaxed, and it largely obviated screwing

The eye to be examined was under cycloplegia and moreover surface anaesthesia had been applied by Novesine® 0 4% eye drops

The contact glass was placed in the conjunctival fornices and was filled with Methocel®

At the free end of the contact glass the transducer was placed (cf Fig 4 1) lightly supported by an assistant who also supervised the axial direction of the sound beam by inspecting the echograms on the screen (Fig 4 4)

Good echoes from the four acoustic interfaces in question (Methocel anterior corneal surface aqueous humour anterior lens surface, posterior lens surface vitreous body and vitreous body retina) were taken as a guarantee of the axial direction as even slight deviations from the direction immediately reduced or eliminated the echo from the posterior lens surface

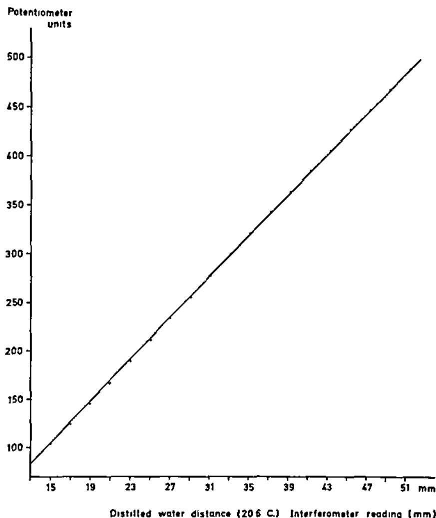


Figure 4.3 An occasional *interferometer water calibration* of the ultrasound measuring potentiometer

In all cases I was personally responsible for the fine adjustment and reading in potentiometric units of the distances between the ocular echoes on the screen At least five readings were done for each eye The mean values for the three partial distances in the eye were then converted to the corresponding eye lengths on the basis of conversion tables worked out after each calibration This gave the axial chamber depth (including the central corneal thickness) the lens thickness and the vitreous length in mm The sum of all three gave the axial length



Figure 4 4 *The measuring conditions*

Interferometer calibration was repeated after any repair of the ultrasound equipment and also at even intervals throughout the study period At each ocular measurement the calibration was checked on the basis of the distance between repeating echoes from a steel test block

With a well-established technique a trained assistant and a cooperative child the entire procedure took only a few minutes and the disparity between repeated measurements was slight Ten successive measurements in one session showed the following conformity expressed in the standard deviation from the mean

Axial length	SD ± 0 057 mm
Chamber depth	SD ± 0 052 mm
Lens thickness	SD ± 0 062 mm
Vitreous body	SD ± 0 062 mm

The reproducibility within the study period may be illustrated by four sets of measurements (A – D) on an emmetropic person carried out at intervals of 3 6 months

	A	B	C	D
Chamber depth (mm)	2 7	2 9	2 8	2 9
Lens thickness (mm)	4 8	4 7	4 7	4 7
Vitreous body (mm)	16 0	16 0	15 9	16 0
Axial length (mm)	23.5	23 6	23 4	23 6

Discussion

Let us consider below the sources of error which may manifest themselves in all stages of the measuring process

Transducers

The ideal sound beam for oculometry is narrow and parallel A divergent sound beam affords less concentration of energy more absorption and less resolution at right angles to the axis Accordingly it is considered important to operate within the near field of the transducer (P) expressed by the formula

$$P = \frac{D^2 - \lambda^2}{4\lambda}$$

D signifies the crystal diameter and λ the wavelength of the pressure waves emitted A higher frequency is tantamount to shorter wavelength and to a larger near field A short wavelength also improves the axial resolution

A number of oculometric studies have been performed with theoretically un suitable transducers In the case of the plane transducer (4 mHz 5 mm) used by Jansson (1963) for instance the near field is only a little over 16 mm consequently the sound beam is divergent when it gets to the posterior pole of the eye This applies also to other studies despite higher ultrasonic frequencies and longer near fields as part of the near field has been used *in front of* the eye because of interposed liquid in a contact glass

The acoustic interfaces in the eye are not plane but convex or concave and even with a narrow sound beam there may be doubt as to the exact source of a recorded echo Such factors were advanced especially by Gernet (1963) who suggested that the posterior wall echo moved farther forward – at an estimate 0.3 mm – than the level through the bottom of the concavity When analysing ocular refraction a further correction was made according to the distance between the anterior retinal surface and its rod and cone layer and lastly some adjustment of calibration was included (Franceschetti & Gernet 1965) Their total correction factor for axial length was 0 6 – 0 9 mm depending on the refraction value Others have rejected the need of correcting for concavity in the posterior pole (Buschmann 1964 and 1966 Nover & Grote 1965) – This of course influences comparison of various oculometric studies some authors having used corrections and others not

That transducers of theoretically varying suitability have nevertheless afforded fairly consistent values might be explained by the study of Kosoff & Robinson (1967) who analysed the distribution of intensity in the sound beam within the near and far field In plane transducers there will be a marked concentration of energy in the geometrical axis with an abrupt fall at the sides In practice the weak par axial parts of the sound beam are of no major importance as a certain amount of *reflected energy is a prerequisite for recording good echoes on the screen* With a suitable sensitivity the *effective* sound beam therefore is narrow and axial — i e better than indicated by the diameter of the transducer (and the length of the near field)

The Ultrasonolux transducer used by me is supposed to secure a narrow sound beam with good resolution In addition the slight focusing can compensate for the divergent acoustic effect of the ocular lens The transducer is designed so as to allow direct ophthalmoscopic control of the direction towards the macula but this pos sibility was not utilized I share Oksala s (1967) view that the transducer is fairly difficult to use in examining the fundus but very useful in biometry even without ophthalmoscopy

Liquid filled Contact Glasses

In principle all types of contact glass may cause pressure deformity of the eyeball The same applies to the weight of the water or methocel column generally used in front of the cornea As already mentioned several workers have therefore preferred measuring the anterior chamber optically and the remaining axial distance by ultra sound and if so usually with the transducer coupled direct to the anterior corneal surface by a drop of Methocel

The contact glass used by me rests on the extralimbal sclera by an annular foot plate whose concavity corresponds to the scleral convexity Thus the cornea itself is only exposed to the pressure of the Methocel column The weight of the light Ultrasonolux transducer is transmitted to the walls of the contact glass through its slightly conical shape (cf Fig 4 1)

The liquid distance between the transducer and the cornea is about 13 mm This affords

(1) the desired complete separation of the initial echo and the echo from the *anterior corneal surface moreover*

(2) shifting of the target zone away from the first part of the screen where linearity was not ideal in my calibrations

(3) greater assurance that the direction of examination corresponds to the desired axial one (cf Pallin 1969)

Apparatus

Oksala (1967) stated that ultrasonic equipment may differ so much in general that the results are hardly comparable This applies particularly to diagnostic ultrasono

graphy in which the appearance of abnormal sound reflections depends entirely upon the sensitivity and dynamic range conditioned by a given constellation of apparatus and transducer It has proved difficult to standardize the sensitivity Buschmann (1966) used oil as his reference medium Ossoinig (1968) a so-called tissue phantom consisting of citrated blood However a low sensitivity also influences the oculometric results Some energy is absorbed during lens passage and owing to the loss of energy the rear wall echo may originate not from the vitreo retinal interface but from the anterior aspect of the sclera or even farther back This has been clearly demonstrated in an experimental study by Buschmann (1964) and the influence upon measuring results in patients has been shown by Itin & Brawand (1968)

Oscilloscopic Tracing

The echogram on the screen appears when the energy reflected from the tissues is recorded by the transducer intensified, and modulated But there are limits to the accuracy with which oscilloscopes display amplitude (ordinate) and time (abscissa of more interest in our context) Kosoff & Robinson (1967) reported an accuracy of only three per cent They also emphasized that slim well-defined echoes on the screen result from 'limiting envelope detection and differentiation An unmodulated echo complex usually includes several wavelengths The stronger the reflection (and/or amplification) the wider the unmodulated echo and consequently its beginning will appear earlier on the screen When using a 12 mHz transducer for instance three wavelengths amount to a difference of 0.38 mm and even more when using lower ultrasonic frequencies Therefore even slight changes of amplification or direction of the sound beam may decisively alter the point on the screen where the echoes start A modulated echo on the other hand is depicted as a narrow well defined reflection which permits convenient reading in oculometry The modulation depends entirely on the apparatus the user cannot feel sure but can only hope that the position corresponds to the maximum intensity of the unmodulated echo

With my equipment and measuring technique I could not demonstrate definite changes in chamber depth or lens thickness related to the relevant variations in sensitivity This might vary a bit from measurement to measurement judging by the appearance of a reliable posterior wall echo Especially in the case of long myopic eyes the sensitivity had to be increased

Reading of Echograms

Instead of a potentiometric scale the more recent standard equipment has electronic time marking which is photographed with the axial echogram On the basis of polaroid photos the axial lengths are calculated The evident advantage is the snapshot which allows reading on the basis of four simultaneously reflected echoes In my experience however it is difficult to read with the accuracy of 0 1 mm generally stated by authors using this reading technique Decimal reading is rendered dif

ficult because due to the parallactic distortion in the outer zones of the screen the axial echogram and time marking have to be condensed to some extent Incidentally the method is rather expensive to apply in major series when upholding the demand that the findings for each eye have to be confirmed by several polaroid photos

The method used by me involves the advantage that the measuring unit of the potentiometer represents less than 0 1 mm eye distance and that adjustment and reading are easy and reproducible Its drawback is of course possible changes in the echogram caused by the time — though short — which elapses while measuring from echo to echo This inaccuracy is reduced by the demand of at least five sets of readings in each eye I have also had newer equipment at my disposal (Kretztechnik 7100 with electronic time marking and polaroid camera) but found the older unit more accurate and more convenient (Fledelius & Alsbirk 1973)

Conversion to Ocular Dimensions

Comparison of various materials is possible because nearly all workers — after calibration to something physically well-defined — have used the mean velocities of ultrasonic propagation in ocular media determined by Jansson (1963) Of course there are individual divergences from these normal values but they hardly exceed ± 1 2% (Jansson 1963 Coleman et al 1973) In addition changes of ageing may be operative especially as regards the lens However this can hardly apply to the present homogeneous series of children in whom gross changes of the lens were exceptional (Chapter 11)

Reported chamber depths have varied somewhat Some authors subtract the central corneal thickness Others state direct the quantity measured by echography including the central corneal thickness in chamber depth It is not customary to correct for the higher ultrasonic velocity in the cornea itself (1550 m/sec against 1532 m/sec in the aqueous humour) as such correction would affect only the third decimal

It may be mentioned lastly that some workers have preferred stating eye dimensions in time units (μ sec) as in fact we are measuring time differences on the screen (Gerstner 1966 Poujol 1970) In clinical studies however it is considered more relevant to state ocular dimensions in mm than to leave the conversion to the reader

Patient Factors

In examining children in particular it is important to ensure *a uniform state of accommodation.* In practice this means cycloplegia since otherwise there may be variations in lens thickness and chamber depth Cycloplegia also obviates the theoretical source of error that in the case of a small pupil iris tissue may influence the site of the echo from the posterior limit of the anterior chamber

The measurement of chamber depth and lens thickness may also be affected by the *patient s position.* Chamber depth is believed to increase in the supine position the weight of the lens entailing a slight shift backwards This is mentioned because a few workers have used a set-up in which the patient is not lying but sitting

On the Total Accuracy in Ultrasound Oculometry

Jansson (1963) Oksala (1964) and Pallin (1969) reported an accuracy of 0 1 0 2 mm in ocular ultrasonography According to Gernet & Franceschetti (1967) "the total margin of error for the axial length hardly exceeds 0.3 – 0 5 mm if one proceeds subtly" Oksala (1967) stated that modern equipment allowed measurement with an error of around ½% In repeated axial measurements Lowe (1968) found variations up to ± 0.3 mm.

Baum (1967) made greater demands on accuracy and criticised the ultrasonic equipment available for ocular use Nevertheless he admitted that "in view of the degree of accuracy of ultrasonic eye measurements achieved by other investigators using less refined techniques and equipment it would appear that ultrasonic measurement of the axial length is not critical because the eye is nearly a sphere and acceptable measurements are obtained as long as a true diameter is used for measure ment In this connection it should be pointed out also that the individual variations in ocular dimensions completely overshadow the less marked fluctuations due to the apparatus that may occur *within* as well as *between* the various materials (Fledelius & Alsbirk 1973)

In most ultrasound publications the measurements are given with two decimals This suggests an accuracy which is not actually present From a calculation point of view however the explanation is that the numerical values represent means of a set of measurements on eyes and/or groups of individuals In statistical assessments based on mean values moreover it is considered fair enough to include at least the second decimal Coarse rounding up or down might reduce or potentiate differences and thereby influence the significance calculations – On my own data cards I have listed chamber depth and lens thickness with two decimals but the longer measure ments for vitreous and axial length with one Two decimals are systematically given in all the tables listing the measuring results (Chapter 6)

Concluding Remarks

After an account of the oculometric ultrasound technique used in the present study possible sources of error are discussed Such errors may manifest themselves in all links of the measurements Differences due to method are no doubt operative from material to material but nevertheless oculometric studies have shown good mutual agreement

The present material is of homogeneous composition comprising children around 10 years of age All were examined under cycloplegia and under uniform

conditions on the whole – thus also subject to the same error of method The main emphasis is laid on comparing the various groups and sub-groups of the material, but at the same time the results contribute to our knowledge concerning the refrac tion components during growth (Chapter 6)

CHAPTER 5

REFRACTION

Refraction findings in the premature group and in the control group of full term children of the same age will be compared below after an initial survey on the refraction pattern and its alterations during growth First previous publications on children in general and prematures in particular will be reviewed

Review of the Literature

Refraction Pattern During Childhood

A distinction is made in the literature between *longitudinal (prospective) series* and *cross sectional studies* (e g Sorsby et al 1961) In longitudinal studies the same children are followed for a number of years In cross-sectional studies different age groups are examined at the same time – in the hope that random samples will reflect the age variation

Longitudinal refraction studies afford more guarantee of establishing the actual changes in a group One of the most thorough projects in this line is Hirsch s (1952 1964 etc) Ojai study comprising 1200 Californian school children followed from the age of 5 years

The Ojai project has supplied important data concerning individual refraction changes during school age but it also reflects the difficulties involved by longitudinal studies on a major scale In the first place a large number dropped out and only about 40% of the children could be followed up to the age of 14 a fact that has influenced the representativeness of the material Another drawback is that the determination of refraction had to be performed by different examiners including relatively untrained students Moreover the retinoscopic method can hardly be considered reproducible, the examination was carried out in physiological relaxation not under drug induced cycloplegia

Finally it may be asked in general what the analysed group of Californian school children represented No mention is made of the social and racial composition of the population substructure or of the admission criteria to the school(s) con

cerned Thus a certain not further specified part of the population was not included in the sample

These factors apply universally to school series — The influence of social re cruiting factors — even within the same urban area — is apparent from int al Danish population studies on squint (Frandsen 1960) and myopia (Goldschmidt 1968)

Information about refraction and its changes during growth has also been sub mitted by the studies of Sorsby and his associates from 1961 (Refraction and its components during the growth of the eye from the age of three) The material comprises predominantly British school children partly a small fraction followed longitudinally and partly a larger quota forming the basis of a cross sectional study The authors admit that the selection for the project (volunteering) did not make it ideally representative

Other studies on this aspect have been chiefly cross sectional based upon material from eye clinics refraction clinics and ophthalmological practitioners (Wibaut 1926 and 1932 Betsch 1929 Brown & Kronfeld 1929 Kronfeld & Devney 1931 Jackson 1932 Tron 1934 Slataper 1950) — or non-ophthalmological material (Larsen 1971) Existing literature on the subject is on the whole inhomogeneous loaded by differences in method definitions geography and race making it dif ficult to gain a total impression

Above most emphasis has been laid on considerations regarding the nature of the various refraction series It is not reasonable to discuss here in more detail the results of the individual studies on which I have based the following condensed view on the refraction pattern during childhood In part fairly recent reviews are available (e g Sorsby et al 1957 Goldschmidt 1968 Duke Elder 1970 and Sorsby 1972) and in part the present study is concentrated particularly on prematures In addition to the authors already mentioned the following may be added (in chronological order) Steiger 1895 and 1913 Sourasky 1928 Sorsby 1934 Sato 1941 and 1968 Castren 1955 Sorsby et al 1961 and 1970 McLaren 1961 Molnar 1961 Zilberman 1963 Gernet 1964 Tait 1966 Goldschmidt 1969 Gernet & Olbrich 1969

In brief it may be emphasized The average infant is born with hypermetropia between 2 and 4 dioptres During the first years of life a gradual reduction takes place *and at 7 years of age refraction is between + 1 0 and + 2 0 D The tendency* towards myopia continues accentuated during prepuberty and the growth spurt of puberty which is attained earlier by girls than by boys while later the sex difference is largely eliminated In adolescents the mean refraction is in the range + 0 5 to *+ 1 25 D and only a small proportion (10 20%) have developed actual myopia*

In neonates the distribution of refraction values corresponds approximately to a Gaussian curve (Wibaut 1926) situated on the hypermetropic side of 0 whereas in adults the refraction spectrum shows a marked concentration (excess) of values around the above mentioned slightly hypermetropic mean value At the same time most races develop a skewness towards myopia

The initial part of the age curve has been questioned by some authors (Brown & Kronfeld 1929 Brown 1936 and 1938 Slataper 1950 and Andree 1964) who reported increasing hypermetropia from birth up to the age of 6 years before the usual reduction sets in As this has been based upon *eye clinic materials* the explana

tion is possibly a relative preponderance of squinters whose *latent* hypermetropia might decrease with advancing age (and glass correction) So far however the discrepancy between the outlined courses of development has not been satisfactorily explained

Where *astigmatism* is concerned the great majority of children have low (physiological) astigmatism with the rule" Changes are minimal during growth but for the sample the tendency is towards reduction of the total number of dioptres with the rule (Jackson 1932 Hirsch 1963) Mild degrees of astigmatism predominate in the refraction range around emmetropia High ametropia is more often associated with major degrees of astigmatism (Lang 1920 Kronfeld & Devney 1930)

The refractive state in *Danish school children* has been studied by several recent authors Engbæk (1969) found myopia in 1.3% of 7 8 year-old school children (n = 1 768) Øster & Kjærgaard (1964) in 4 4% of 8 12 year-olds (n = 2,229) and Johansen (1950) in 8 2% of 12 15 year-old schoolboys (n = 527) In Goldschmidt s (1968) large school material (n = 9,243) the prevalence of myopia was 9 5% in 13 14 year-olds somewhat higher among girls than boys – It applies to all these school series that only children with impaired vision or other ocular complaints were re ferred to an ophthalmologist and an exact refraction diagnosis was made only in this fraction There has been no systematic refraction study of uselected Danish samples and the *whole* spectrum of refraction values cannot be specified

Refraction in Prematures

The refraction pattern in prematures has been investigated in a number of studies to be reviewed below On this basis it may be estimated (1) that most prematures seem *to follow the normal pattern and (2) that the deviations from normal are at the* myopic end of the spectrum However it is difficult to form a quantitative im pression of the relationship between "normals" and deviants

The term myopia of prematurity has followed in the wake of literature on *retrolental fibroplasia (RLF) and gradually – though still questioned – seems to have* become established Thus it is beyond doubt that eyes affected with RLF are most often permanently myopic (King 1950 Reese & Stepanik 1954 Krause 1955 McNeil 1956 Gregory 1957 Weekers et al 1961 and others)

Birge *(1956) reported seven cases of moderately severe myopia in surviving* prematures in whom ophthalmoscopy disclosed a fundus characterized by myopia or mild degrees of cicatricial *RLF The term myopia of prematurity was suggested* for this type of myopia which was unusual in that it did not progress after its initial occurrence *Shortly* after Alfano *(1958) submitted another series of seven* children with myopia at pre school age six had weighed ≤ 1300 g at birth

In a follow up of school children who had weighed ≤ 1816 g (4 lbs) at birth (n = 233) Zacharias et al (1962) demonstrated a definitely increased frequency of myopia but only in that part of the series *(one third) that had exhibited signs of* active RLF during the first months of life The presence as well as the degree of myopia were correlated to the severity of the early retinal changes during the phase

of active RLF Of the remaining two thirds who had not shown retinal affection neonatally, only 4% were myopic

Incidentally the myopia of prematurity has been discussed by a number of authors who will be mentioned below in an order according to the age of the children when examined

Refraction in Prematures During the Neonatal Period

Gleiss & Pau (1952) found 11 myopics among 23 newborn prematures Four re mained myopic beyond the first months of life Oxygen therapy had not been ad ministered

Fletcher & Brandon (1955) found a typically high but very fluctuating myopia in small prematures during the first month of life (n = 462) However only 22 re mained highly myopic (5%) In 19 of the 22 permanently myopic children there was ophthalmoscopic evidence of RLF

In Neuman s (1963) series of 200 premature infants 9 5% were myopic

Graham & Gray (1963) studying 150 newborn prematures and 98 control infants born at term, found a definite tendency towards myopia in prematures A similar tendency was reported by Grignolo & Rivara (1968) and by Mathew & Sawney (1970) while in Molnar s (1961) study this tendency was slight

However the great inaccuracy of retinoscopy in newborns – and especially prematures – must be borne in mind The problems are posed by the infant being in an incubator by the common use of blepharostats (Khodadoust et al 1968) and by opaque refractive media in a number of cases

Refraction in Prematures During Pre school Age

In studies on the ocular status of 3 5 year-old prematures Wagner (1957) found 27% (n = 104) and Møller (1970) more than 9% myopics (n = 640), both findings clearly above normal in this age range Kalina (1969) reported six cases of cicatricial RLF among 43 children of a birth weight ⩽ 1300 g Of the remaining 74 eyes in 37 children 7 were myopic These authors had no control series

In children aged 3 years Lomickova (1964) found approximately the same incidence of myopia in samples of premature and of mature children but the degree of myopia was higher among the former A control group was also available in the study of Jain & Garg (1970) who demonstrated a clearly increased incidence of myopia in an Indian group of prematures – even though 80% of the children had been of a gestational age ⩾ 38 weeks

Other publications deal with congenital myopia and pre school myopia which like myopia of prematurity is of early onset relatively high and most often station ary According to Hiatt et al (1965) myopia detected before school age must be assumed to have been present from birth Their material comprised 166 children with early myopia 13% of whom were premature Curtin (1963 and 1970) examined

66 children with congenital myopia 34% had been premature but half of them also had a familial predisposition to myopia All 66 had a conus (posterior sclerectasia) and in Curtin s opinion such eyes might represent an arrested stage in the development of retrolental fibroplasia"

Among a large series of birth weight ≤ 1816 g (n = 1 128) McDonald (1967) found pre school myopia in 3% one third of whom also exhibited signs of RLF

In many cases the terms myopia of prematurity pre school myopia and congenital myopia seem to signify the same thing Indeed the last mentioned *type* is usually diagnosed at a *later* stage of childhood but is nevertheless considered congenital

Refraction in Prematures During School Age

Castrén s (1955) study of 480 prematures and 216 mature controls showed a relatively low incidence of *myopia* viz 3 7% and 2.3% respectively Among the prematures however myopia was somewhat more common in the groups having the lowest birth weight In a series of prematures McLaughlan (1963) found 12% myopics among those whose birth weight had been below 1500 g as compared with 3% in the total group of prematures (n = 281) Janus Kukulska (1962) studying surviving school children whose birth weight had been ≤ 1250 g (n = 67) found 21% myopics half of whom had myopia exceeding -6 D Zacharias et al (1962) have already been quoted above (p 49)

With regard to the occurrence of *astigmatism and anisometropia* the results have been conflicting Castrén (1955) was unable to demonstrate a significant difference between the premature and control group Wagner (1957) on the other hand reported a high prevalence among prematures but had no control series

The Literature on Refraction in Prematures May be Summed up as Follows

The general order of Nature favouring refraction in the vicinity of emmetropia seems to be disturbed in at least a certain proportion of surviving prematures The result is often *myopia.*

It is a typical finding that several of the cases are congenital or early (pre school) usually of a high dioptric value but fairly stationary i e without the marked tendency to gradual progression typical of the more common types of myopia of later onset

As a rule all degrees of cicatricial RLF result in permanent myopia Early myopia in prematures without a hereditary predisposition may represent the sequel to RLF which has otherwise regressed

This included
(a) Retinoscopy under cyclopentolate tropicamide cycloplegia
(b) Subjective control of the retinoscopic refraction value
(c) Keratometric measurement of corneal astigmatism

Retinoscopy is usually considered the objective – and therefore reliable – method of assessing refraction as it is *not* based upon the patient s estimate and statements However this objectivity merely consists in transferring the subjective estimate from the untrained patient to the trained examiner, this involves a more standardized inaccuracy The retinoscopic standard error is recognized particularly when the findings are routinely checked by a subjective refraction determination in connection with the retinoscopy Duke Elder (1969) estimated that the experienced examiner s margin of error was 0 25 D Others have found a greater inaccuracy (Nordlow 1949 Safir et al 1970 Hyams et al 1971)

In the present study the refraction value was determined as the *spherical equi valent in dioptres* calculated as the mean value of the retinoscopic findings in the two main meridians In all cases the retinoscopic finding was checked by subjective acceptance of the glass while the child was still under cycloplegia

Cycloplegia. Atropine is the classical cycloplegic agent Residual accommodation – an indirect measure of the efficacy of the cycloplegia – has proved less after atropine than after other cycloplegics cf e g Bothman (1932) and Sorsby et al (1955) Due to its attendant inconvenience viz the prolonged paralysis of accom modation atropine is not well-suited for refraction studies like the present one Besides it requires regular instillation through several days a demand hard to fulfill in an out patient study Lastly it is a matter of discussion whether the refraction finding after atropine is optically the most true or whether it represents an un physiological state (Duke Elder 1969) – cf that most clinicians rarely prescribe glasses with the full atropine value

Instead the modern fast acting cycloplegics have come into extensive use At present cyclopentolate hydrochloride (Cyclogyl®) is the agent of choice instilled several times at intervals of a few minutes In the course of 20-30 minutes it affords satisfactory cycloplegia which subsides entirely in a few hours and thus involves a minimum of inconvenience (Rasgorshek & McInture 1955 Milder 1961 Gettes & Belmont 1961 Miranda 1972) The cycloplegia is most complete in eyes with light irides Miranda (1972) therefore suggested supplementing it with tropicamide eye drops (Epitromin® Mydriacyl®) for brown-eyed subjects

In the present material I used Cyclogyl® 0 5% instilled twice or thrice at a few minutes intervals and Epitromin® once or twice Retinoscopy was performed in 25 30 minutes immediately followed by the subjective test with glasses As a rule there was agreement within ± 0 25 D In the event of a difference between the two sets of values the retinoscopic finding was corrected according to the subjective value in cooperative children

Incidentally the material was well-suited for the use of fast acting cycloplegics

All the children were of the white race (the predominant majority of Scandinavian (Danish) descent) and nearly 90% had light iris colour (Chapter 12)

Keratometry The keratometric findings served as my basis of whether the child was to be classified as astigmatic This was done mainly because of my demand of subjective confirmation of the retinoscopic finding A reliable subjective confirmation was the rule among children who were *a priori* wearing glasses for somewhat higher degrees of astigmatism but not among those with low degrees of astigmatism For this group cylindric glasses according to the retinoscopic findings were often rejected by children unused to spectacles

Owing to these considerations I simplified the problem in the final analysis to comprise only the corneal astigmatism Normally it is the most important contribution to the total astigmatism of the eye and the keratometric findings are extremely accurate and reproducible Below *corneal astigmatism of one dioptre or less will be considered physiological whereas values above one dioptre will be designated astigmatism.*

Present Results

The findings will be grouped as follows

(a) Results for the total premature and mature groups
(b) Supplementary analyses of the sub-group of myopic children
(c) *A total survey on the final refraction diagnoses in the material*

Results for the Total Premature and Mature Groups

Refractive Values (Spherical Equivalent)

Table 5 1 lists the data for the two main groups – prematures and matures For both there is an accumulation of values around emmetropia and low hypermetropia (comprising the range from 0 to + 1 9 D) This tendency is further emphasized in Table 5 2 in which the data are given in three classes *myopia* (all eyes with negative refraction) and *high hypermetropia* (+ 2 0 D and over) on each side of the *middle group* (0 – + 1 9 D) which comprised almost three-quarters of the eyes

Table 5 2 is also divided by sex The most striking difference between the groups was found on comparing premature and mature boys In this case the size of the two marginal refractive groups indicates a relative shift to the left in the refractive state of the prematures viz fewer hypermetropic and more myopic eyes

The same impression is gained from Fig 5 1 which depicts the percentage frequencies among the respective groups of children Fig 5.3 (p 70) moreover sets out the values for the mature children This figure does not include the prematures since apart from the small myopic tail the graph was so close to the distribution among the mature children (cf Table 5 1)

In previous refraction series it has been customary to state the mean value with

Table 5 1 *Cycloplegic refraction values* (spherical equivalents) in the premature and mature group
Number of eyes (left columns) and percentages (right columns) in one dioptre refraction classes

	Prematures n = 300		Matures n = 237		All eyes (right+left) distrib in per cent	
	right eyes	left eyes	right eyes	left eyes	premature n = 600	mature n = 474
+ 6 0 and higher	1	1	2		0 3%	0 4%
+5 0 +5 9 D	2	3	4	4	0 8%	1 7%
+4 0 - +4 9 D	3	2	6	7	0 8%	2 7%
+3 0 - +3 9 D	11	12	10	12	3 9%	4 6%
+2 0 +2 9 D	23	26	17	19	8 2%	7 6%
+1 0 - +1 9 D	119	116	96	93	39 2%	39 9%
0 +0 9 D	100	101	79	81	33 5%	33 8%
-0 1 -1 0 D	21	19	10	10	6 7%	4 2%
-1 1 - -2 0 D	8	9	6	2	2 8%	1 7%
-2 1 -3 0 D	3	3	2	6	1 0%	1 7%
-3 1 -4 0 D	4	3	3	1	1 2%	0 8%
-4 1 - -5 0 D	1		1	1	0 2%	0 4%
-5 1 - -6 0 D		1		1	0 2%	0 2%
-6 1 - -9 0 D	2	3			0 8%	
Myopia exceeding 9 0 D	2	1	1		0 3%	0 2%

standard deviation as also shown in the first part of Table 5.3 However these quantities were not used in the statistical assessment of differences between the groups as the premises of parametric significance calculation were not sufficiently fulfilled The premature as well as the mature group showed fully significant deviations from the normal distribution as well as leptokurtosis and skewness towards myopia (both calculated as advocated by Snedecor & Cochran (1967)) Furthermore there was

Table 5 2 *Distribution of eyes* (right and left pooled) *on three main refraction groups* (left columns) and *range* of refraction values (right column) for premature and mature eyes (top) and further sub-divided by sex (*bottom*)

Frequencies in per cent Number of eyes in parentheses

	Myopia (negative re fraction values)	Emmetropia and low hyper metropia (0 - + 1 9 D)	Hyperme-tropia + 2 0 D and higher	Range of refraction values (in dioptres)
Premature eyes n = 600	13 3% (80)	72 7% (436)	14 0% (84)	- 17 0 + 8 0
Mature eyes n = 474	9 3% (44)	73 6% (349)	17 1% (81)	- 10 0 - + 6 5

Premature boys n = 298 eyes	*13 4%*	*71 8%*	*14 8%*	*17 0 - + 8 0*
Mature boys n = 226 eyes	*7 5%*	*72 6%*	*19 9%*	- 5 0 + 6 5
Premature girls n = 302 eyes	13 3%	73 5%	13 2%	- 6 5 - + 5 5
Mature girls n = 248 eyes	10 9%	74 6%	14 5%	- 10 0 - + 6 0

variance inhomogeneity between several of the groups (F test) – It is evident also that the relative preponderance among the prematures of eyes with *high* myopia must decisively influence the mean value as well as the standard deviation

Supplementary to the impression of a central tendency in the groups Table 5.3 gives the *median refraction values* (i e the 50 percentile in the groups) The result was exactly the same median for all groups viz + 1 0 D On the face of it this

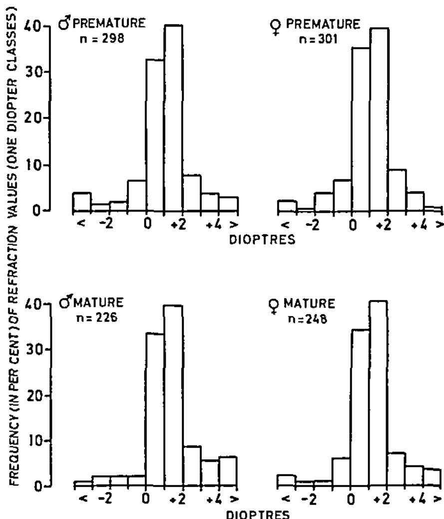


Figure 5 1 Frequencies (in per cent) of *retinoscopic refraction values* (in one-dioptre classes) in premature boys and girls (top) and mature boys and girls (bottom)

The marginal columns in the histogrammes comprise all values below –3 0 D (left) and above +4 0 D (right) n refers to number of eyes

would seem surprising but it is due to the purely practical factor that despite the even biological transitions the refractive values could be given only with fixed intervals due to the limitations of the measuring method Therefore all eyes stated to have the refractive value + 1 0 D in fact represent the range ± 1/8 D around the value + 1 0 Regard was paid to this in Table 5.3 by stating the *corrected medians* calculated as for pooled data For the premature group having + 0 94 D the corrected

median value was about 0 1 D lower than for the mature children i e a considerably less marked difference than suggested by the mean values

Thereafter the groups were compared mutually using the non parametric Mann Whitney test The refractive values for the prematures differed just significantly from

Table 5 3 *Mean ocular refraction values and standard deviations median refraction values and "corrected medians* (see text) *and correlation coefficients r between refraction values of right and left eyes* - in premature and mature groups (top) and further subdivided by sex (bottom)

	Mean ocular refraction (in dioptres) Standard deviation in parentheses		Median refraction (P_{50}) in dioptres "Corrected median" in parentheses		Correlation co-eff r between refraction values of right & left eyes
	right eyes	left eyes	right eyes	left eyes	
Prematures n = 300	+ 0 73 (1 93)	+ 0 77 (1 88)	+ 1 0 (+ 0 93)	+ 1 0 (+ 0 94)	0 58
Matures n = 237	+ 1 06 *(1 61)*	+ 1 08 *(1 44)*	+ 1 0 *(+1 03)*	+ 1 0 *(+1 05)*	*0 84*
Premature boys n = 149	+ 0 66 (2 42)	+ 0 78 (2 28)	+ 1 0 (+ 0 94)	+ 1 0 (+ 0 98)	0 52
Mature boys n = 113	+ 1 22 *(1 44)*	+ 1 20 *(1.51)*	+ 1 0 *(+ 1 03)*	+ 1 0 *(+ 1 06)*	0 90
Premature girls n = 151	+ 0 80 (1 27)	+ 0 77 (1 38)	+ 1 0 (+ 0 92)	+ 1 0 (+ 0 90)	0 80
Mature girls n = 124	+ 0 91 (1 74)	+ 0 97 (1 37)	+ 1 0 (+ 1 03)	+ 1 0 (+ 1 04)	0 82

Table 5 4 *Refraction values in the premature group subdivided according to the birth weight limits 1500 and 1750 g*
Frequency of myopia in per cent mean values (in dioptres) and standard deviations (in parentheses) median values (in dioptres) and corrected medians (in parentheses)

Premature children birth weight groups	Frequency of myopia as percentage of all eyes	Refraction mean value and standard deviation in parentheses (in D)		Refraction median value corrected median in parentheses (in D)	
		right eyes	left eyes	right eyes	left eyes
Birth weights ≤ 1500 g n = 89	17%	+ 0 36 (3 03)	+ 0 68 (2 07)	+ 0 75 (+ 0 80)	+ 1 0 (+ 0 88)
Birth weights 1501 1750 g n = 93	14%	+ 0 82 (1 34)	+ 0 70 (2 30)	+ 1 0 (+ 0 88)	+ 1 0 (+ 0 89)
Birth weights > 1750 g n = 118	10%	+ 0 93 (1 01)	+ 0 90 (1 25)	+ 1 0 (+ 0 99)	+ 1 0 (+ 0 98)

those of the matures, in the case of the right eyes of the two groups p = 0 036, of the left eyes 0 05 (two-sided test) This was due primarily to the boys Comparison of premature and mature boys revealed a difference in the distribution of refractive values by p = 0 028 for the right eyes but p was greater than 0 05 for the left eyes (p = 0 073) Among the premature and mature girls compared mutually the p values were as high as 0 40 and 0.30 for the right and left eyes respectively It may be concluded that the shift towards lower (more myopic) refractive values which the total premature group appeared to show in relation to the mature group (assessed on the basis of mean values and corrected median) was only barely significant at the 5 per cent level After grouping by sex this difference was demonstrable only in the boys – and only for the right eyes

The last column of Table 5.3 lists the *correlation coefficients between the refractive values of the right and left eyes* The two eyes were in general highly correlated in this respect The only deviation was in the premature boys who had a less marked right left correlation This affected the result to such an extent that in the total premature group too the correlation became significantly less marked than in the mature group

Table 5 4 gives the frequency of myopia as well as the mean refraction and the median refraction in the premature group divided according to the birth weight limits 1500 and 1750 g There seems to be a tendency to a more common occurrence of myopia with lower birth weight group but the differences between the three birth weight groups were not significant according to the Kruskal Wallis test (χ^2 = 0 94 and 0 88 for the right and left eyes respectively) The same result was found by a (non parametric) calculation of the correlation between birth weight and refractive values The highest degree of positive correlation was found for the sub-group of premature boys right eyes but here too the r_s value (0 083) was not significant – In other words it was not possible to demonstrate a significant correlation between birth weight and refractive value when using – as above – the data for the total premature group in the calculations

Anisometropia

As a rule the refractive values for the two eyes are very close together A difference between the two sides may be expressed in two ways

(a) By simple subtraction stating direct the extent of the anisometropia in dioptres
(b) By calculation of the correlation between the right eyes and left eyes in major series

Correlation coefficients for the present material were listed already in Table 5.3 and commented in relation thereto

Table 5 5 gives the occurrence of various degrees of anisometropia in the material Anisometropia of 2 dioptres and over was found in 11 of the prematures (n = 300) and in 8 of the mature children (n = 237) Of nine prematures having anisometropia exceeding two dioptres 7 were boys and 2 girls Only one of these 9 children had been more than 1750 g at birth Within the premature group there were five cases of purely myopic anisometropia all in children ≤ 1500 g at birth

Table 5 5 Degrees of anisometropia in the premature and mature group Numbers and percentages (in parentheses) in five side-difference classes

Numerical values of right left eye differences (in dioptres)	Premature group n = 300		Mature group n = 237	
0 0.25 D	240	(80%)	203	(85 7%)
0 5 0 75 D	42	(14%)	15	(6 3%)
1 0 1 75 D	7	(2 3%)	11	(4 6%)
2 0 3 75 D	6	(2%)	6	(2 5%)
4 0 and higher	5	(1 7%)	2	(0 8%)

Side differences of less than one dioptre in the refractive values were considered physiological This applied to the great majority of both groups Only 30 children (less than 6% of the total material) had anisometropia exceeding one dioptre Among them 11 were myopic in both eyes and 13 hypermetropic in both eyes Six had mixed anisometropia In 16 of the 30 children the eye differing most from emmetropia was myopic

The groups with anisometropia were on the whole too small to afford statistically valid deductions on the basis of the differences related to prematurity/maturity

Astigmatism

The various degrees of corneal astigmatism measured by keratometry are set out in Table 5 6 80% of the prematures and roughly 85% of the mature children had physiological values defined here as astigmatism of one dioptre or less Astigmatism exceeding one dioptre was found in 19 7% and 14 5% respectively The difference is not significant ($p > 0\ 1$ X^2–test) Table 5 6 also demonstrates that the distribution

Table 5 6 *Corneal astigmatism* in the material as measured with the Javal Schiøtz keratometer in the premature and mature group (top) and in the premature group subdivided according to the birth weight limit 1500 g (bottom)
Incidences in per cent

	Physiological corneal astigmatism (i e 1 D or less)	Corneal astigmatism 1 25 2 5 D	Corneal astigmatism above 2 5 D
Prematures n = 269	80 3%	18 0%	1 7%
Matures n = 237	85 5%	12 6%	1 9%
Prematures of birth weight 1500 g and less n = 80	66 9%	29 4%	3 7%
Prematures of birth weight above 1500 g n = 189	86 0%	13 2%	0 8%

of the keratometric values in prematures of a birth weight > 1500 g ($n = 189$) was almost identical with those in mature children Actual deviation was found only for the group of prematures weighing ≤ 1500 g ($n = 80$) one third of these children had corneal astigmatism exceeding one dioptre which is significantly more frequent than the 14% applying to the remaining part of the premature group ($p < 0.01$ χ^2–test) 6% and 8% respectively of the children examined by keratometry in the premature ($n = 269$) and mature group ($n = 237$) had *no astigmatism* defined here as a difference of 0 25 D or less between the two corneal main meridians

Where astigmatism amounted to 0 5 D and over its axes could be reasonably established *Astigmatism with the rule* was predominant i e cases with the higher corneal refractive power in the vertical meridian or close to it Within both main groups more than 86% of all children assessed by keratometry had astigmatism with the rule

Oblique astigmatism – the main meridians deviating by more than $\pm 10°$ from $90°$ or $180°$ – was found in less than 8% of the prematures and less than 6% of the mature children In the birth weight group ≤ 1500 g there was a somewhat higher frequency – 12% – of oblique astigmatism but the preponderance compared with the remaining premature group was not significant

The keratometric values in the right and left eye were closely correlated For all sub-groups of the material the correlation between the radii of curvature (expressed for each eye as the mean between the radii of curvature measured keratometrically in the two main meridians) are given by the correlation coefficient 0 99 The *degree* of corneal astigmatism too was on the whole the same on both sides in the same individual A side difference exceeding 0.5 D was observed in only 10 premature and 10 mature children A total of only 7 children – rather more than 1 % of all those assessed – had a side difference of more than one D

From the above data it may be concluded that the prematurity did not prove to exert any obvious influence upon the degree of corneal astigmatism There was no significant difference between the distributions in the premature and in the mature group However there was a trace of some influence as children of the lowest birth weight group (≤ 1500 g) had more often higher degrees of astigmatism than the remaining children of the premature group

Supplementary Analyses of the Sub-group of Children with Myopia

The predominantly negative conclusions above do not rule out the possibility that *sub-groups* may show evidence of a relationship between low birth weight and refraction It would be natural here to focus attention on the children with myopia. Therefore to clarify matters further some results will be submitted below *only for the myopic children* This applies to four items The degree of myopia the correlation between birth weight and refractive value the time of onset of myopia and the hereditary predisposition to myopia

Degree of Myopia

The terms low and high will refer to the degree of myopia Higher myopia thus means numerically higher dioptric findings – synonymous with more negative refractive values

In both main groups of the material the myopia was predominantly low Values of –2 0 D and lower were found in 71% of the myopic eyes in the premature group (n = 80) and in 64% of the myopic eyes in the mature group (n = 44) Truly high myopia was rare Myopia exceeding –6 0 D was found in 8 premature eyes two of which belonged to the same child, while in the other six there was anisometropia with unilateral high myopia Among the mature children only one eye had myopia higher than –6 0 D

Within the premature group certain trends became apparent when the children were grouped by birth weight limits 1500 and 1750 g Myopia exceeding –2 0 D was more common (50% n = 30 myopic eyes) in the group with birth weight ≤ 1500 g than in the other two birth weight groups of prematures (5 out of 26 myopic eyes in the birth weight group 1501 – 1750 and 3 out of 24 myopic eyes in the birth weight group over 1750 g) When the latter two were pooled the fraction was 16% (8 out of 50 myopic eyes) and the difference from the 50% in the lowest birth weight group thus significant ($p < 0\ 01$ X^2–test) The difference remained significant though only at the 0 05 level when the calculation was based upon number of individuals instead of number of eyes with myopia

It may be concluded that the various degrees of myopia showed almost identical distributions in the premature and mature groups However high myopia was relatively more common among the prematures where 8 out of 80 myopic eyes exhibited values exceeding –6 0 D as compared with only 1 out of 44 mature eyes with myopia However the numbers involved are small and the confidence ranges show wide overlapping – Within the premature group the lowest birth weight group (≤ 1500 g) showed a significant shift towards more myopic values assessed in relation to the remainder of the premature group

Correlation Between Birth Weight and Refractive Value

A non parametric correlation analysis was carried out on the sub-group of premature children with myopia Spearman s rank correlation coefficient (r_S) was calculated for the right the left and the right + left eyes in myopic boys and girls separately

In a two-sided significance test the result for the right eyes in premature boys (n = 21) was a t value with $p < 0\ 05$ and for the right + left eyes (n = 40) even significance at the 0 01 level In the other four sub-groups the t values were not significant However on a working hypothesis that the lowest birth weights are correlated to the highest degrees of myopia it is not unreasonable to use one sided significance testing The result now is that in five of the six myopic sub-groups there was a significant correlation at least at the 0 05 level The only exception was the left eyes of the premature girls

It is concluded that in the case of premature myopic children there was a positive correlation between birth weight and refractive value The correlation was most marked in the case of premature myopic boys and it was only for the left eyes of premature girls with myopia that no relationship could be demonstrated – On the other hand the correlation was so slight that it was not manifest when considering the *total* premature group (cf p 59) – numerically predominated by unaffected children showing a "normal" refraction pattern

Time of Onset of Myopia

On the hypothesis that prematurity may cause myopia a higher fraction of *early* cases would be expected among the prematures than among the mature children Such cases would then be manifest as early as the first year of life since the underlying mechanisms are assumed to be analogous – or identical – with those in RLF

In retrospective studies however it is difficult to ascertain the exact time of onset of myopia Even pronounced refractive anomalies often remain undetected until the first medical examination at school and most cases of myopia discovered even that late have presumably been present for a long time Hiatt et al (1965) were quoted above (p 50) as having expressed this view based int al upon the predominantly static nature of congenital myopia

Therefore it was analysed how large a proportion of the present myopias could be classified as pre school myopia i e diagnosed during early childhood or possibly when starting school at the age of 6 7 years In the premature group there were 27 such eyes in 15 children In the mature group there was only one eye with early myopia Thus out of the myopic eyes in the premature group (n = 80) 34% could be interpreted as early – as compared with only 2% of the myopic eyes in the mature group (n = 44) The findings are further elaborated in Table 5 7 Almost two-thirds of the myopias in the birth weight class ≤ 1500 g were classified as pre-school myopia a significantly higher fraction than in the higher birth weight groups of prematures

Table 5 8 specifies the refraction data for the 15 prematures with pre school myopia The table shows the time at which the ametropia was definitely diagnosed In 10 of the 15 cases it had been recognized about the age of 4 or earlier There were many cases of anisometropia and in 9 of the 15 children the anisometropia amounted to more than two dioptres – All 15 children had been followed by repeated ophthalmological examinations It was characteristic that all cases were static

Table 5 9 sets out the degree of myopia in three sub groups pre school myopia of prematures (n = 27 eyes) school myopia" of prematures (n = 53 eyes) and myopia in matures (n = 44 eyes) There was a significant difference between the distributions in the three groups (compared two and two mutually in χ^2 tests) The group of pre school myopia in prematures included fewest low and most high myopias Reversely the premature myopias that had set in after the age of 7 were predominated by very low values The myopic eyes of the mature group were in between but also with a predominance of low values

Table 5 7 *Number of myopic eyes* (first column) *and percentage thereof dis covered before the age of seven* (second column) in subgroups of the material
Top premature and mature group Bottom subdivisions of the pre mature group by birth weight limits 1500 and 1750 g

	Total number of myopic eyes	Frequency (in per cent) of pre-school myopia in the total group of myopic eyes Number of eyes in parentheses	
Prematures n = 600 eyes	80	34%	(27)
Matures n = 474 eyes	44	2%	(1)
Prematures of birth weight $\leqq$ 1500 g n = 178 eyes	30	63%	(19)
Prematures of birth weight 1501 1750 g n = 186 eyes	26	19%	(5)
Prematures of birth weight > 1750 g n = 236 eyes	24	13%	(3)

The results indicate that the *surplus* of myopic eyes in the premature group as compared with the mature group is due to the fraction of pre-school myopia The prevalence of myopia would have been 9% in the premature as well as in the mature group if eyes with pre-school myopia had been excluded Thus there was evidence to interpret the group of myopia in the prematures as composed of two parts (a) the cases related to the prematurity ('lesional ') which proved to be predominantly static (about one third of all the myopic eyes) and (b) the ordinary myopias setting in at a later stage of childhood and tending to progress This latter group was entirely predominated by low dioptric values In comparison the myopic eyes of the mature group showed somewhat higher degrees of myopia It may be assumed that those premature children who did *not* develop early ('lesional") myopia as a result

Table 5 8 Schematic presentation of *some clinical features in 15 children of the premature group with uni or bilateral pre school myopia*
The last column refers to the case histories (Appendix)

Case records	Sex	Birth weight in g	Age when myopia was first diagnosed	Static or progressive myopia	Refraction values of right & left eyes at the present age (sph/cyl)	Further clinical comments see case histories
12051	♂	1350	3 years	static	-0 5 -4 0	No 6
30173		1470	2 years unilateral high myopia	static	- 14 0 + 1 5	No 8
31637	♂	1200	when starting school	static	-4 0 -1 0	No 10
41732	♂	1400	when starting school	static	-6 75 - 0 5 0 -3 00 - 0 5 0	No 11
42293	♀	1800	2 years	static	+2 5 -6 5	No 12
50195	♂	1750	3 years	static	+1 5 -17 0	No 13
50278	♀	1300	4 years	static	-4 0 -1 0 - 1 0 105	No 4
50772	♂	1250	1 year	static	-8 0 - 2 0 0 -9 0	No 3
50929	♀	1900	4 years	static r e progr l e	-3 0 - 0 5 90 -3 25	No 14
51577	♀	1600	when starting school	one diopt progression in 3 years	-4 5 -6 0	No 17
51699	♂	1300	3 years	static	-1 0 - 1 0 20 -6 0 - 1 0 0	No 18
51723	♀	1500	1 year	static	-4 0 -3 0	No 2

(Table 5 8 cont overleaf)

Table 5 8 contd

Case records	Sex	Birth weight in g	Age when my opia was first diag nosed	Static or progressive myopia	Refraction values of right & left eyes at the present age (sph/cyl)	Further clinical com ments, see case histories
51766	♂	1350	5-6 years	static	-14 0 -2 5 -0 75 90	No 5
60385	♀	1450	4 years	static	+0 75 -3 5 30 +0 75 -3 5 0	No 19
60848	♂	1650	6 years	static	-2 0 -1 0 90 -2 0	No 20

Table 5 9 *The myopic eyes of the material classified by refraction values (in dioptres) Three subgroups are considered (a) Prematures with pre school myopia (b) prematures with school myopia and (c) matures (not further subdivided only one eye had myopia considered of pre school origin)*
Numbers shown

	Myopic eyes		
	Premature group		Mature group
	"Pre school" myopia n = 27 eyes	"School" myopia n = 53 eyes	(not sub-divided) n = 44 eyes
-0 1 -1 0 D	5	35	20
-1 1 -2 0 D	2	15	8
-2 1 --3 0 D	3	3	8
-3 1 -4 0 D	7		4
-4 1 -5 0 D	1		2
-5 1 -6 0 D	1		1
-6 1 -9 0 D	5		
Myopia exceeding -9 0 D	3		1

of their prematurity had to be considered slightly retarded in general development – judging by their relatively fewer dioptres of myopia – as compared with the children of the mature group.

Myopia and Hereditary Predisposition

Lastly, it was endeavoured to elucidate whether the differences in the incidence of myopia between the premature and mature group were explicable wholly or partly by data concerning inherited predisposition. An exhaustive answer to this question would require family studies of an extent outside the scope of the present project. Instead, an estimate was based upon the data supplied by the person who accompanied the child at the examination. Some parents had brought detailed information about the spectacles worn by the child's siblings or other close relatives; in other cases the relatives who accompanied the child were examined on that occasion. However, the main rule was a general uncertainty concerning the information supplied. The person who attended the child was always closely questioned about eye diseases in the immediate family, including refractive anomalies. The immediate family was broadly taken to mean the proband's siblings, parents, parents' siblings, and grandparents.

The result of this analysis is shown in Table 5.10. It was not possible to demonstrate significant differences between the premature and mature group. In both

Table 5.10 *Hereditary predisposition to myopia*, according to information given by parents in the premature group and the mature group, the children of both groups divided according to the presence of myopia. Number of children, incidences in per cent.

		Myopia known among immediate family for
Prematures n = 302	with myopia n = 45	11 (24%)
	without myopia n = 257	49 (19%)
Matures n = 237	with myopia n = 24	12 (50%)
	without myopia n = 213	40 (19%)

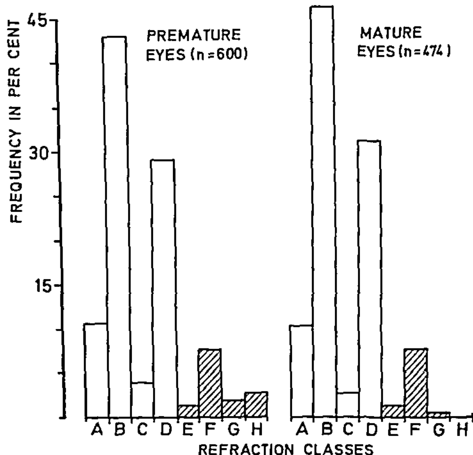


Figure 5 2 *Final refraction diagnoses* in 600 eyes of prematures (left) and 474 eyes of mature children (right) Frequencies in per cent Myopic classes are hatched

A hypermetropia and astigmatism
B hypermetropia without astigmatism

C emmetropia and astigmatism
D emmetropia without astigmatism

E school myopia and astigmatism
F "school myopia without astigmatism

G pre school myopia and astigmatism
H pre-school myopia without astigmatism

there was information about myopia in the immediate family of about 20% of the children As regards the children with myopia in the two main groups 24% of the premature (n = 45) and 50% of the mature myopes (n = 24) had a positive family history The difference is not significant at the 0 05 level when X^2 is calculated with Yates correction Within the premature group there was not a significant difference in hereditary predisposition among the myopic and the non myopic children where as the mature group showed a predisposition significantly more often in the fraction with myopia ($p < 0.01$ X^2–test) The prematures with pre-school myopia did not differ in this respect from the remainder of the premature fraction with myopia. In 3 of the 15 prematures with pre school myopia there was a family history of myopia

However the numbers involved are on the whole small and the quality of the data not optimal *It seems reasonable to conclude merely that in the premature* group it was not possible to demonstrate a preponderance of hereditary predis position as an essential cause of the higher incidence of myopia within this group

The Final Refraction Diagnoses

In Fig 5 2 *the refractive findings in the material are collected It shows in columns* the percentage frequencies of the various refraction diagnoses for all eyes in the pre mature group (n = 600) and in the mature group (n = 474) The diagnoses were based upon retinoscopy plus keratometry Eyes with a spherical equivalent between 0 and + 1 0 D were considered *emmetropic* without however including the latter border line in the group All eyes with a spherical equivalent of + 1 0 D or higher were considered *hypermetropic* and all eyes in which the spherical equivalent was negative were considered *myopic* The latter were sub-divided on the basis of previous oph thalmological examinations into *pre school myopia* and its counterpart the more common *school myopia* The addition *astigmatism* refers to a keratometric finding of a difference exceeding one dioptre between the main meridians

About 55% of all eyes in the material were *hypermetropic* and of those about one-quarter had *astigmatism.* About 33% of all eyes were classified as *emmetropic* and of them just over one tenth had *astigmatism.* The remainder of the eyes almost *12% were myopic* and one fourth *also astigmatic*

It is evident from Fig 5 2 that the *pre school myopia* among the prematures constitutes the only striking difference between the two column graphs The other three refractive groups – hypermetropia emmetropia and *school myopia* – showed a fairly uniform distribution in the two groups of children and the same applied to astigmatism Astigmatism was more common in the marginal refraction groups than in the group with emmetropia

Discussion

Several factors have been commented already in the review on the literature and discussed in presenting methods and results

Here *the refractive values in the present material will first be related to a few previous refraction studies* It proved difficult to find publications entirely suited for comparison They should deal with representative series of children preferably of the same age – and not with the more common eye clinic materials

Fig 5 3 depicts two classical refraction curves (Brown & Kronfeld (1929) and Sorsby (1934)) compared with a refraction curve from the present series The latter is based upon the 474 eyes of the mature group but broadly speaking it represents the distribution in the total material The curve of the prematures – not traced here

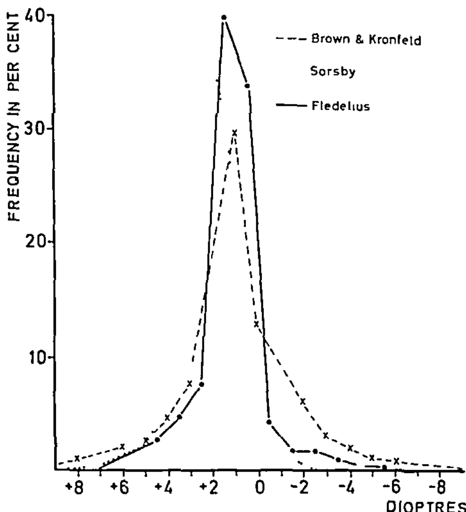


Figure 5.3 *The refraction curve* (relative incidences in per cent) of 474 eyes from the mature group of the present material compared with the refraction curves of *Brown & Kronfeld* (1929, based on adolescents less than 25 years old) and of *Sorsby* (1934 based on 672 non Jewish children aged 4 8)

– ran a course close to that of the matures from which it differed only by its some what bigger myopic tail

Sorsby s (1934) curve was based upon the refractive values in 672 unselected non Jewish children aged 4 – 8 years examined under atropine cycloplegia This was the control group in a study designed to investigate the pre myopic state in Jewish children who are more prone to myopia at a time before myopia (and near work) arises These children were an average of 4 years younger than the present ones The two refraction curves run an almost parallel course but Sorsby s is shifted about one dioptre towards hypermetropia This is presumably due partly to the age difference and partly to differences in the depth of cycloplegia (Sorsby using atropine)

Brown & Kronfeld s (1929) refraction curve is based upon a somewhat older age group viz adolescents up to 25 years examined after instillation of atropine Theirs was an *eye clinic material* and this fact as well as the older age presumably explains the shift towards myopia as well as the wider shape of the curve with a relatively large number of ametropias

The only material having an approach exactly analogous with mine is Castrén s (1955) which also comprised a premature group and a control group He arrived at the conclusion that the refractive values showed no significant differences between the groups and indeed this is not at variance with the tendency in my material The essential *difference* between the two sets of results concerns the small fraction of prematures in whom it seemed reasonable in the present material to relate myopia to prematurity Castrén could not distinguish such myopia of prematurity His ma terial consisted predominantly of "large prematures only 23% having weighed less than 2000 g at birth – the upper limit in my group of prematures Incidentally the two materials differ so much in a number of respects that direct comparison of the results is difficult Apart from the difference in birth weight criteria there are differ ences in age distribution facilities for neonatal treatment method of determining refraction etc Further Castren did not present his raw data merely the refraction diagnoses some of which (emmetropia anisometropia astigmatism) were even de fined in a way somewhat different from the usual Therefore it was not possible on the basis of the information given to convert Castrén s data to a form comparable with e g the present material

Astigmatism

This field within refraction anomalies is characterized by a lack of generally accepted definitions of the various types of astigmatism One of the reasons is the difficulty in measuring the astigmatism in practice

Astigmatism is due to deviations from the spherical shape of the ocular refractive surfaces relevant to retinal image formation This may apply to all refracting surfaces in the eye but only the astigmatism of the *anterior corneal surface* can be measured clinically with fair accuracy The contribution of other surfaces viz the *residual astigmatism* is calculated indirectly as the difference between the corneal and the total astigmatism The *total astigmatism* may be assessed subjectively as well as

objectively In early materials in particular, it has been assessed *subjectively* How ever this implies a marked psychological factor Many patients initially resist any change in the accustomed visual impression even though it is optically for the better (cortical astigmatism Sorensen 1944) *Objective* evaluation is by retinoscopy but this method too carries its inaccuracies

It is generally agreed that the anterior corneal surface makes the most important contribution to total astigmatism but it is also agreed that keratometry alone is not enough However opinions differ concerning the extent and role of the residual astigmatism Jackson (1932) estimated that frequently it amounted to more than half the corneal astigmatism while others have found it to be of less importance For instance Tait (1966) studying intraocular astigmatism in children arrived at the result that lenticular astigmatism was hardly of any importance in 90% the keratometry and retinoscopy agreed within 0 5 D

Experience from the present material is in keeping with Tait s (1966) As al ready mentioned (p 53) I based my statements of astigmatism exclusively upon the keratometric findings classifying all corneal astigmatisms of one dioptre and less as physiological This limit has been suggested by int al Kronfeld & Devney (1930) and owing to its rather wide margin it pays regard to the modifying residual astig matism The same margin ensures that most people fall within the physiological range According to Steiger (1895) and Kronfeld & Devney (1930) among others a *mean* difference between the refractive power in the two main corneal meridians is expected to be 0 5 – 0 75 D in the general population

With regard to the orientation of the corneal main meridians I have acted in accordance with Lang (1920) who analysed a large number of glass prescriptions in a hospital material with a special view to the placement of the cylinder axis He found the stronger refractive corneal meridan to be mainly in the ranges 80 – 100° (with the rule) and 170 – 190° (against the rule) These limits were used in analysing my own results When the main meridians were situated outside these two ranges the astigmatism was designated as oblique I found no instances of irregular or bi-oblique astigmatism

The somewhat varying classifications of astigmatism by different authors intro duce a factor of uncertainty in comparisons The results of the present study are in agreement with practically all the named studies in this field except to some extent Jackson s (1932) and especially Castrén s (1955) Castrén found astigmatism in only 4-6% of the children despite a *lower* limit (keratometric astigmatism of 0 5 D) towards what was considered physiological

Possible Aetiological Factors

The question whether the differences in refraction are due to genetic or to exogenous actions cannot be definitely answered by the present material On the basis of Table 5 10 however it does not seem reasonable to ascribe the relative preponder ance of myopia in the prematures (the early cases) to genetic factors (Refraction is presumably transmitted by multifactorial inheritance (Grützner et al 1970))

Among possible exogenous factors I studied – with a negative result – the role of the following maternal pregnancy factors *Toxaemia anaemia and excessive smoking* Children from such "loaded" pregnancies showed *higher* (more hyper metropic) mean refractive values than children of pregnancies that must be con sidered uncomplicated These three items like the two below were not presented in the section on results but are briefly mentioned here in connection with possible aetiological factors (cf also Chapter 14)

I could not demonstrate any influence of *neonatal jaundice* either The serum bilirubin levels were equally often elevated in the premature sub-groups of myopics and non myopics In the *clinical assessment of the newborn infant s condition* how ever there was a significant difference between the same two groups (at the 0 05 level) 43% of the myopic and 25% of the non myopic prematures were deemed "mildly or severely affected" The corresponding values are not listed for the mature group as its sub groups are too small for further assessment

However the clinical state at birth is closely related to birth weight – there being most infants in a poor condition in the group with the lowest birth weight. This suggests that prematurity as such is responsible for the difference in refraction between the prematures (with their fraction of pre school myopia) and the children of the mature group

Summary and Conclusions

The refraction curves (relative frequency of the various refractive values) exhibited for the premature as well as the mature group significant *leptokurtosis* in the range corresponding to the mean and the median refraction as well as a significant *skewness towards myopia.* These findings accord with refraction curves reported by others

It was the object of the analysis to elucidate any differences in refraction be tween the premature and mature group However tabular surveys column graphs and figures leave the main impression that the refractive pattern was fairly uniform in the two groups The main difference affected *the myopic part of the spectrum. In this range there was a preponderance of prematures* (13.3% as compared with 9.3% myopia in the matures) evident especially among the boys

This tendency was confirmed statistically The total distribution of refraction values in the prematures differed significantly (towards myopia) from that of the matures for the right as well as the left eye but only at the 0 05 level The same applied to the right eyes in the group of boys However the left eyes in the boys and all eyes in the girls did not show significant differences related to prematurity/ maturity

Mean values and corrected median values were around + 1 0 D but lower for the prematures than for the matures – and lowest for the premature boys This sub group showed the highest standard deviation and also the lowest correlation co-efficient between the refraction values in the right and left eyes These findings indicate that *in premature boys the development of refraction is particularly vulner able*

A total of 80 premature and 44 mature eyes were myopic The myopia was higher in the prematures and in one third of these eyes (27 eyes in 15 children) it had been diagnosed in early childhood This condition is termed *pre school myopia.* It is characterized by its static nature the fairly high values and the tendency to anisometropia Among the mature eyes with myopia only one had pre school myopia The incidence of ordinary school myopia setting in after the 6th – 7th year of life was the same in the premature and mature group (9%)

The influence of birth weight could be proved in the group of *premature eyes with myopia* A one sided significance test revealed *a correlation between birth weight and refraction values.*

The role of birth weight was apparent also in the fact *that the lowest birth weight group (≤ 1500 g) stood out as the one having most refraction anomalies* This group included relatively more eyes with pre school myopia high myopia and astigmatism

In relation to the remaining premature group the sub-group of *premature myopics* showed *a preponderance of children who had been characterized neonatally as clinically affected* This again may be related to the low birth weight

In looking for possible contributory explanations of the excess of myopics among the prematures it was *not* possible to demonstrate any influence of maternal toxaemia anaemia or excessive smoking during pregnancy or to the degree of neonatal jaundice in the infant Judging by information supplied about a family history of myopia there were no differences in genetic predisposition between the two main groups

On the basis of the findings the myopic children of the premature group comprised two fractions (a) early cases which must be related predominantly to the prematurity as such and (b) *ordinary juvenile myopia* The latter group as a whole showed significantly lower degrees of myopia than the myopics of the mature group When disregarding pre school myopia this may be taken as the refractive sign of delayed general somatic development in the prematures

All considered the values found support the hypothesis of a 'myopia of prematurity It is not possible to point out aetiological causes other than the trauma of prematurity

CHAPTER 6

REFRACTIVE COMPONENTS

> There must exist other factors in the eye whose variations closely keep pace with that of the cornea We still know too little about the optical constants of the eye to be able to decide what it is that varies with the cornea but in all likelihood it is axial length
>
> (M Tscherning 1886)

The dimensions of the growing eye were not elucidated in much detail until the advent of ultrasound oculometry Previous methods (based upon optical phakometry *and Rushton s X-ray principle respectively cf Chapter 4) required* a cooperation which is rarely obtainable from children The results obtained by the various methods have been recapitulated by int al Sorsby et al (1957 1961) and Larsen (1971)

Review of the Literature

Ocular dimensions around the age of 10 years have been studied only sporadically but information may be gained from an empirically approximated ocular growth curve as shown in Fig 6 1 It represents a cumulative survey of the increase in axial length with age based on my assessment of the oculometric studies to be quoted below

The initial part of the curve is based partly upon measurements of eyes removed from dead foetuses (Ehlers et al 1968) partly upon ultrasonic measurements on live born prematures (Grignolo & Rivara 1968) Full term newborns were studied by Gernet (1964) and Luyckx (1966) the increase in axial length during childhood by Sorsby et al (1961) Sorsby & Leary (1970) Gernet & Hollwich (1968) Gernet (1969) Bechetoille & Saraux (1970) Saraux & Bechetoille (1971) and Luyckx &

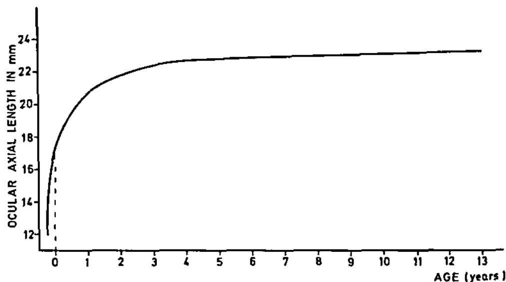


Figure 6 1 Ocular axial length from the gestational age of 6 7 months to the age of 13 years *An empirical growth curve of the eye* based on several European materials (see text)

Delmarcelle (1971) Larsen (1971) and Pérez Llorca (1971) have contributed by measurements of all age groups from birth to puberty

Most of the publications have stated mean values in various age groups during childhood In other words the curve in Fig 6 1 was in fact traced between a number of scattered points determined by cross sectional projects, except in the case of a small proportion of the children in the two studies by Sorsby et al (1961 and 1970) and the follow-up study reported by Saraux & Bechetoille (1971) According to these longitudinal series the majority of children exhibit only a very slight annual increment in axial length In a small proportion however the ocular growth rate is faster a finding entirely consistent with the refractive changes in the corresponding age groups (Hirsch 1961 Sorsby et al 1961)

A certain dispersion around the growth curve outlined in Fig 6 1 is due to differences in methods and materials – factors already discussed at length in Chapters 4 and 5 Only a few items will be briefly recapitulated below

Differences in Method

The results of Sorsby et al (1961 1970) were based upon optical phakometry Comparison with ultrasonic measurements revealed good agreement when the eyes were small whereas a considerable discrepancy was apparent for the less common long eyes

In the other studies quoted in relation to Fig 6 1 the measurements were performed by ultrasound but the conditions of measurement and the principles of calculation nevertheless varied

Where measuring conditions are concerned it may be mentioned that the demand of cycloplegia was waived by Luyckx & Delmarcelle (1971) in children older than 6 and by Pérez Llorca in all age groups Indeed these studies showed greater axial thickness of the lens than in other materials without drugs it was apparently difficult to neutralize the strong accommodation impulse in the children

Gernet (1964) compensated for the possible corneal deformity by adding 0.3 mm to the values measured in the newborns Like Luyckx (1966) and later also Bechetoille & Saraux (1970) Franceschetti & Gernet (1965) used a correction factor of + 0 6 mm owing to the uncertainty concerning the site of reflection in the posterior pole of the eye Larsen (1971) and Pérez Llorca (1971) did not correct for this while François & Goes (1970) added 0.35 mm (the distance from the internal limiting membrane to the receptors in the rod and cone layer) to attain "la longeur axiale *optique* de l oeil"

Differences in Materials

Sorsby et al (1961) stated right out that their group of children was not a random sample but nevertheless considered their results representative Larsen (1971) tried to ensure random sampling from an ophthalmic viewpoint by selecting his material among children admitted to an E.N T department but the refractive distribution in his material showed a shift towards myopia compared with normal for the age concerned This was even more marked in Bechetoille & Saraux s (1970) material which comprised 100 eyes in boys aged 8 – 12 years among whom not less than 37% were myopic This factor is of course important in evaluating the size and growth *norms* stated In general the myopic eyes have longer axes and a higher growth rate than the much more common rather static eyes with emmetropia and hypermetropia Pérez Llorca (1971) in describing his material merely stated that the children were emmetropic or had "refraction corresponding to their age

The Emmetropic Adult Eye

Growth of the eye is considered to have been largely completed by the age of 13 – 14 years (Weymouth & Hirsch 1950 Sorsby et al 1961 and 1970 Gernet 1964 Delmarcelle & Luyckx Bacus 1971) the exception being the few eyes with progressive myopia

Thus the completion of the growth curve (Fig 6 1) at a 13–year value of 23.3 mm axial length is considered to represent the normal value in adults However the axial length of the emmetropic eye is not a fixed quantity Even the early measurements (Schnabel & Herrnheiser 1895) and optical phakometric calculations (Mauthner 1876 Steiger 1913 Tron 1929 Wibaut 1932 Stromberg 1936 and

others) demonstrated variations in axial length also in eyes having the same re fractive value According to the classical assumption the optical axial length of the emmetropic eye is believed to be about 24 mm and this was the value chosen e g for Gullstrand s schematic eye Subsequent ultrasound measurements have suggested a somewhat lower value Now the mean emmetropic axial length is considered to be in the range 23 0 – 23 5 mm (Yamamoto et al 1961 Franken 1961 Jansson 1963 Gernet 1964 Franceschetti & Luyckx 1966 Nakajima & Kimura 1967 François & Goes 1969 Gernet 1969 Larsen 1971 and others)

Sex Differences in Axial Length

Above the results for both sexes have been considered together In this connection it should be borne in mind that males have longer optical axes than females There is doubt about this sex difference only in newborns – presumably because of the more inaccurate measuring conditions The difference could be established by Luyckx (1966) and by Larsen (1971) but not by Gernet (1964) All other findings indicate a sex difference in axial length of about 0 5 mm in children and adults (Stenstrom 1946 Sorsby et al 1961 Jansson 1963 Gernet 1964 Franceschetti & Gernet 1965 Fridman & Savitskaya 1966 Nakajima & Kimura 1967 François & Goes 1969 Larsen 1971 Delmarcelle & Luyckx Bacus 1971)

Co variation of Optical Components

Present views concerning the origin of ametropia and the variation as well as correla tion of the optical components have been described by int al Sorsby (1964 1972) Therefore no historical account will be given here A number of correlations exist between the various refractive components The most marked one is the correla tion between refraction on the one hand and axial length/vitreous length on the other but a clear correlation between axial length and corneal curvature has been found as well These and other correlations contribute to explaining why refractive values around emmetropia are far more common than might be expected according to Steiger s (1913) then epoch making theory on the accidental combination of normally distributed refractive components

The object of the present study was to elucidate not only ocular dimensions but also the question whether the co-variation of the optical components might prove to be influenced by the prematurity Axial lengths and other optical quantities in *prematures* also after the neonatal period have so far been discussed in only one publication (Grignolo & Rivara 1968) These authors stated that already within the first year of life prematures fully eliminate the neonatal deficit in axial length which is caused solely by the shorter gestational period However they did not follow the same children longitudinally but based their conclusion upon cross-sectional results from numerically small groups

Present Results

The results of the axial ultrasonic measurements and of the keratometric determinations of the corneal radius of curvature in the central optic zone will be reported below These values exhibit by and large a Gaussian distribution (Steiger 1913 Sorsby et al 1957 and others) and unless otherwise stated the statistical assessments were parametric Owing to the close correlation between the values for the two eyes the results and significance calculations reported below are based solely upon measurements of the right eyes

Where *measuring technique* is concerned it may be stated that the ultrasonic results are based exclusively upon the site of the echoes This implies that

(a) central corneal thickness is included in the values for anterior chamber depth and

(b) special correction factors were *not* used for the posterior pole – as did Franceschetti & Gernet (1965) and others

The results were analysed in three sections

(1) Refractive components Mean values and differences between prematures and matures boys and girls

(2) Correlation between refraction and refractive components

(3) Results for some refraction sub-groups in the material

Refractive Components

A survey is given in Table 6 1 which presents the mean values for the right eyes of the fraction of the children who had ultrasound oculometry They numbered 191 – or 64% – in the premature group (69% of the boys and 59% of the girls) and 159 – or 67% – in the mature group (72% of the boys and 63% of the girls) There was satisfactory agreement between the mean refractive values in Table 6 1 and those in Table 5.3 Therefore the fraction studied by ultrasound seems representative of the groups in the total material

Axial Eye Length

Ranges	Premature children	20.5 – 26 9 mm
	Mature children	19 8 – 25 9 mm

Fig 6 2 gives the percentage frequency of various axial length classes in the main groups The histograms show a shift towards shorter axial lengths in

Premature boys as compared with mature boys

Premature girls as compared with mature girls

Premature girls as compared with premature boys

Mature girls as compared with mature boys

This was supported numerically by the mean axial lengths in Table 6 1 The differences were as follows

Table 6 1 *Retinoscopic refraction* (dioptres) *axial ocular dimensions* (mm) *and radius of corneal curvature* (mm) in 191 premature and 159 mature children The values are derived from *right eyes* only
Mean values and standard deviations are shown also in subgroups divided by sex

	Refraction (D)	Axial length (mm)	Depth of anterior chamber (mm)	Lens thickness (mm)	Vitreous length (mm)	Corneal curvature radius (mm)
Right eyes of prematures n = 191	+0 63 ±2 25	23 01 ±0 97	3 82 ±0 25	3 63 ±0 21	15 57 ±0 92	7 69 ±0 30
Matures n = 159	+1 05 ±1 35	23 27 ±0 82	3 82 ±0 25	3 58 ±0 17	15 87 ±0 77	7 87 ±0 26
Premature boys n = 103	+0 58 ±2 82	23 23 ±0 99	3 84 ±0 25	3 62 ±0 20	15 77 ±0 96	7 74 ±0 30
Mature boys n = 81	+1 26 ±1 37	23 39 ±0 92	3 86 ±0 26	3 56 ±0 17	15 97 ±0 86	7 92 ±0 25
Premature girls n = 88	+0 68 ±1 33	22 76 ±0 90	3 79 ±0 23	3 63 ±0 22	15 33 ±0 81	7 62 ±0 30
Mature girls n = 78	+0 82 ±1 31	23 15 ±0 68	3 79 ±0 23	3 60 ±0 17	15 76 ±0 65	7 80 ±0 25
Boys (premature + mature) n = 184	+0 88 ±2 32	23 30 ±0 97	3 85 ±0 25	3 59 ±0 19	15 86 ±0 92	7 82 ±0 29
Girls (premature + mature) n = 166	+0 75 ±1 32	22 94 ±0 82	3 79 ±0 23	3 62 ±0 20	15 54 ±0 77	7 71 ±0 29

Premature boys	<	mature boys	Δ 0 16 mm	(not significant)
Premature girls	<	mature girls	Δ 0.39 mm	(p < 0 01)
Premature children	<	mature children,	Δ 0 26 mm	(p < 0 01)
Premature girls	<	premature boys	Δ 0 47 mm	(p < 0 01)
Mature girls	<	mature boys	Δ 0 24 mm	(not significant)
All girls	<	all boys	Δ 0.36 mm	(p < 0 01)

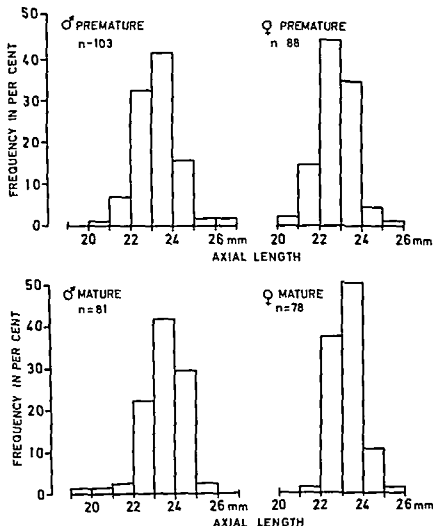


Figure 6 2 *Axial lengths of right eyes* (in mm)
Frequencies (in per cent) in 191 infants of the premature group (top) and 159 infants of the mature group (bottom) subdivided by sex

Thus in the prematures the mean axial length was significantly shorter than among the mature children of the material The difference is 0 26 mm i e of the same range as the sex difference in the groups (mean 0.36 mm) The maturity difference in axial length would have been greater if a correction were made for differences in mean refraction For instance more hypermetropic values are usually tantamount to a shorter axial length a factor to be discussed in detail later in this chapter

Axial Chamber Depth

Ranges Premature children 3 18 – 4 47 mm
  Mature children 3 22 – 4 50 mm

The *mean values* are shown in Table 6 1 There were no significant differences in anterior chamber depth between the children of the premature and of the mature group

There was a slight *sex difference* of 0 05 mm in the prematures and of 0 07 mm in the matures – deeper chambers being found in the boys The sex difference for all girls and boys examined was 0 06 mm – which is significant (p < 0 05)

Axial Lens Thickness

Ranges Premature children 3 12 – 4.22 mm
  Mature children 3 08 – 4 02 mm

The mean value (Table 6 1) was somewhat higher among the prematures than in the mature children (Δ 0 05 mm significant at p < 0 05) The difference was 0 06 mm among the boys and 0 03 mm among the girls – the latter not significant

Among the premature as well as among the mature children the girls had slightly higher mean values than the boys (sex difference 0 01 mm in the premature and 0 04 mm in the mature group) but the differences were not significant at the 0 05 level The same applies to the sex difference calculated for the entire material

Axial Vitreous Length

Ranges Premature children 12 8 – 19.3 mm
  Mature children 12 2 – 18 1 mm

More than 90% of the vitreous lengths measured were distributed in the range 14 – 17 mm

6 8% of the premature and 5% of the mature children had vitreous lengths exceeding 17 mm A vitreous length shorter than 14 mm was found in only six eyes five of which were from the premature group

The mean values in Table 6 1 revealed the following differences

Premature boys < mature boys, Δ 0 20 mm (not significant)
Premature girls < mature girls, Δ 0 43 mm (p < 0 01)
Premature children < mature children, Δ 0.30 mm (p < 0 01)

Premature girls < premature boys Δ 0 44 mm (p < 0 01)
Mature girls < mature boys, Δ 0 21 mm (not significant)
All girls < all boys Δ 0.32 mm (p < 0 01)

These differences are in exact conformity with the results of measuring axial length and indeed this was to be expected on the basis of the high positive correlation between axial length and vitreous length The latter was found to be an average of 0.30 mm shorter in premature than in mature children a difference in the same order of magnitude as the sex difference in the material

Radius of Corneal Curvature

The value for each eye is stated as the mean between the keratometric measurements in the main refractive corneal meridians

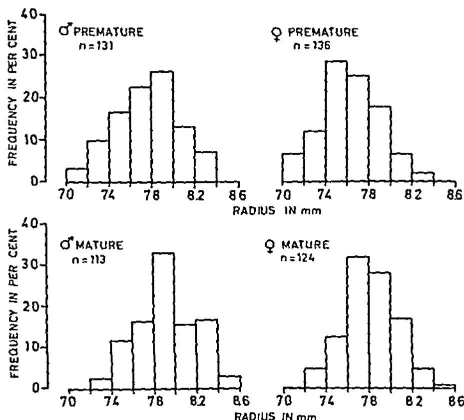


Figure 6.3 *Corneal curvature radius of right eyes* (in mm)
Frequencies (in per cent) of keratometric readings in 267 children of the premature group (top) and 237 children of the mature group (bottom) further subdivided by sex

Range Premature children 6 98 – 8.30 mm
Mature children 7 25 – 8 50 mm

Keratometry was done on 504 of the children 267 prematures and 237 mature children

Fig 6.3 presents the percentage frequencies of the various radii of curvature in the main groups of the material The histograms show a shift towards lower values in

Premature boys as compared with mature boys
Premature girls as compared with mature girls
Premature girls as compared with premature boys
Mature girls as compared with mature boys

Table 6.2 *Corneal curvature radius* (in mm) of right eyes in 267 children of the premature and 237 of the mature group (top) and further subdivided by sex (bottom)
Range mean values and standard deviations

	Number of children	Range of keratometric readings (mm)	Mean radius (mm)	Standard deviation
Prematures	267	6 98-8 30	7 67	0 29
Matures	237	7 20-8 50	7 84	0 26
Premature boys	131	7 10-8 30	7 73	0 29
Mature boys	113	7 20-8 50	7 90	0 27
Premature girls	136	6 98-8 25	7 61	0 28
Mature girls	124	7 25-8 40	7 78	0 23
Boys	244	7 10-8 50	7 81	0 29
Girls	260	6 98-8 40	7 69	0 27

The mean values within the groups are listed in Table 6 2 which comprises all 504 children subjected to keratometry The results correspond quite closely to those in Table 6 1 which was based upon the fraction of the children who also had ultra sonography (a total of 350) The differences between the groups given below are derived from Table 6.2 all were significant at the $p < 0\ 01$ level

Premature boys	<	mature boys	Δ 0 17 mm
Premature girls	<	mature girls	Δ 0 17 mm
Premature children	<	mature children	Δ 0 17 mm

Premature girls	<	premature boys	Δ 0 12 mm
Mature girls	<	mature boys,	Δ 0 12 mm
All girls	<	all boys,	Δ 0 12 mm

Thus the curvature radius of the anterior corneal surface was significantly shorter in the premature group than in the mature children The difference was 0 17 mm viz somewhat greater than the sex difference in the material

Correlation Between Refraction and Refractive Components

Paired Correlations

Tables 6.3 and 6 4 show the correlation matrix for premature and mature children respectively

The variables involved are the refractive value and the five refractive components axial length chamber depth lens thickness vitreous length and radius of corneal curvature Correlation coefficients which did not differ significantly from zero have been omitted Below some of the values in these tables will be emphasized stating the coefficient r of the prematures before that of the mature children

Table 6.3 *Correlation matrix with correlation coefficients r for refraction* (dioptre value) *and refraction components* (in mm) in 191 children of the *premature group*
Correlation coefficients are shown only when differing from zero at significance levels 0 01 (r >0 186) in bold types and 0 05 (r >0 142) in fine types

Axial length	Depth of anterior chamber	Lens thickness	Vitreous length	Corneal radius	
61			**61**		Refraction
	41		**96**	**.56**	Axial length
		.27	**.23**		Depth of ant chamber
			17		Lens thickness
				.54	Vitreous length

Table 6 4 *Correlation matrix for the same parameters as in table 6 3* for 159 children of the *mature group*
Correlation coefficients are shown only when differing from zero at significance levels o ol (r>0 204) in bold types and 0 05 (r>0 156) in fine types

Axial length	Depth of anterior chamber	Lens thickness	Vitreous length	Corneal radius	
- 62	.34		-.56	20	Refraction
	44		.95	.37	Axial length
		31	22		Depth of ant chamber
			- 26		Lens thickness
				.39	Vitreous length

Refraction – axial length	r = –0 61 and –0 62
Refraction – vitreous length	r = –0 61 and –0 57
Refraction – chamber depth	r not signif and –0.34
Refraction – corneal radius	r not signif and 0 20

For the refractive components mutually there were the following significant correlation coefficients still mentioning the prematures first

Axial length – chamber depth	r = 0 41 and 0 44
Axial length – corneal radius	r = 0 56 and 0.37
Chamber depth – lens thickness	r = –0 27 and –0.31
Vitreous length – lens thickness	r = –0 17 and –0 26
Vitreous length – corneal radius	r = 0 54 and 0.39

The correlation matrix for the sub-groups of boys and girls respectively showed broadly speaking the same pattern as in Tables 6.3 and 6 4 Premature boys had on the whole the least marked correlations This applied particularly to the correlation between chamber depth and refraction thereby rendering insignificant the corresponding correlation coefficient for the total premature group All considered it must be concluded that the paired correlations in the prematures did not differ essentially from those in the mature groups

Figure 6 4 *Relationship between ocular axial length (y) and refraction values (x)* in the premature and mature group *Regression lines and correlation coefficients*

Figure 6 5 *Relationship between ocular axial length (y) and refraction values (x)* in the premature and mature groups subdivided by sex *Regression lines and correlation coefficients*

Figs 6 4 and 6.5 lastly set out the association between axial length and re fraction graphically in the form of regression lines the refraction values being the abscissa and axial length the ordinate These curves will be discussed together in a later section of this chapter

Table 6 5 *Stepwise multiple regression between refraction (y) of right eyes and the following 8 variables* Ocular axial length (AL) anterior chamber depth (ACD) *lens thickness* (LT) *vitreous length* (VL) *corneal cur vature radius* (CR) the height of the individual as well as circumfe- rence of skull and age
Only the first two steps are fully specified The variables included and the multiple correlation coefficients are shown also for steps Nos 3 and 4 Finally the multiple r of the ninth step

		Con stant	Step No 1 x_1	Step No 2 x_2	Step No 3 x_3	Step No 4 x_4	Step No 9
Prematures	y =	16 7	- 2 15 AL	+ 4 3 CR	ACD	Age	
n = 191	multi ple r		0 607	0 777	0 816	0 826	0 834
Matures	y =	11 04	- 1 32 AL	+ 2 6 CR	Skull	Height	
n = 158	multi ple r		0 619	0 772	0 782	0 784	0 789
Premature boys	y =	8 61	- 2 58 VL	+ 4 2 CR	LT	Age	
n = 103	multi- ple r		0 691	0 802	0 855	0 868	0 870
Mature boys	y =	12 97	- 1 27 AL	+ 2 3 CR	Skull	Height	
n = 80	multi ple r		0 706	0 801	0 816	0 822	0 825
Premature girls	y =	11 54	- 1 50 AL	+ 3 0 CR	LT	Age	
n = 88	multi ple r		0.580	0 784	0 791	0 800	0 808
Mature girls	y =	14 04	- 1 46 AL	+ 2 6 CR	LT	Height	
n = 78	multi ple r		0 596	0 763	0 770	0 774	0 789

The correlation coefficients given above express quantitatively the co-variation of the refractive components However the analyses have only comprised two para meters at a time assessed in pairs i e without paying regard to other perhaps closer (joint?) associations For this reason the calculations were supplemented by an analysis of the stepwise regression between refraction and a number of parameters which might influence it directly or indirectly A total of nine parameters were included viz the refractive value and the five refractive components (axial length (AL) chamber depth (ACD) lens thickness (LT) vitreous length (VL) and corneal curvature radius (CR)) and in addition height circumference of skull and age

Refraction being the dependent variable was designated y the other eight (x_1 x_2 x_3 etc) were included according to the programme used (BMDO2R Dixon 1971) in a sequence determined by their contribution to the cumulative correlation The latter was expressed by the multiple correlation coefficient (multiple r) The first step included was to enter the variable (x_1) which afforded the best two-sided correlation with the refraction value thereafter the one which most augmented the cumulative correlation Thus multiple r increases numerically in value from step to step in the analysis

On the background of the oculometric dimensional deficit described above two items were of particular interest Did premature and mature children differ (1) in the sequence in which the independent variables were included? and (2) in the multiple r increment from step to step in the analysis? The results are given in Table 6 5

In nearly all these groups *axial length* showed the closest correlation to refrac tion and was thus entered as x_1 The only exception was that of premature boys in whom vitreous length replaced axial length but these two variables had a strong mutual correlation (r = 0 96) In all the groups the *corneal curvature radius* was entered as x_2 whereas the variables of the next steps were included in varying sequence

It is apparent also from the table that the multiple r was raised to its final value (0 79 – 0 87) almost exclusively by the first two steps all subsequent steps con tributing but little to the cumulative correlation

The total assessment of the correlations in the main groups afforded no evidence that prematurity essentially influenced the usual correlation pattern of the optic components

Refractive Sub-groups in the Material

On the basis of the oculometric differences between the main groups the question naturally arises Whether the dimensional deficit of the prematures (axial length vitreous length and corneal curvature radius) expresses a *general* influence upon ocular growth and development or whether it is perhaps due to a minority having more extreme refractive values The latter possibility might be suggested by Table

6 1 which shows for refraction higher standard deviations for the prematures than for the mature children Therefore the groups will be curtailed in some ways below

(a) *Primarily the more extreme refractive values will be omitted*

This leaves reasonably large residual groups around emmetropia – and affords a possibility of clarifying in more detail the most normal part of the two groups

Table 6 6 lists all right eyes showing refractive values in the range –1 0 to +2 5 D viz 163 premature and 139 mature eyes or 85% and 87% respectively of the eyes measured in the groups The differences between the groups proved to be consistent with the corresponding findings from Table 6 1 with the important exception that by virtue of the selection the refraction was practically identical in the sub groups On this background too it could be established that axial length and vitreous length

Table 6 6 *Retinoscopic refraction* (D) *axial ocular dimensions* (mm) and corneal curvature radius (mm) in *right eyes* of 163 children of the premature and 139 of the mature group Mean values and standard deviations
The results are confined to right eyes with refraction values in the range from -1 0 D to + 2 5 D

		Refraction (D)	Axial length (mm)	Depth of anterior chamber (mm)	Lens thickness (mm)	Vitreous length (mm)	Corneal curvature radius (mm)
Right eyes around emmetropia	Prematures n = 163	+0 89 ±0 68	22 97 ±0 80	3 84 ±0 24	3 61 ±0 21	15 51 ±0 68	7 69 ±0 31
	Matures n = 139	+ 1 00 ±0 68	23 31 ±0 63	3 83 ±0 23	3 58 ±0 17	15 90 ±0 62	7 87 ±0 25
	Premature boys n = 85	+0 93 ±0 70	23 21 ±0 75	3 88 ±0 25	3 60 ±0 19	15 73 ±0 70	7 75 ±0 30
	Mature boys n = 68	+ 1 07 ±0 65	23 51 ±0 63	3 87 ±0 22	3 57 ±0 17	16 07 ±0 62	7 94 ±0 24
	Premature girls n = 78	+0 85 ±0 65	22 70 ±0 77	3 80 ±0 23	3 63 ±0 22	15 27 ±0 68	7 63 ±0 31
	Mature girls n = 71	+0 94 ±0 70	23 11 ±0 57	3 79 ±0 23	3 59 ±0 17	15 73 ±0 57	7 81 ±0 25

in the prematures was 0.3 – 0 4 *mm shorter* and the corneal curvature radius 0 18 mm shorter than in the mature children The differences are significant at the 0 01 level Chamber depths and lens thicknesses on the other hand remained practically equal As in Tabl• 6 1 the sex differences were in the same range as the differences related to maturity The boys axial chamber depths were 0 08 in excess of the girls ($p < 0\ 01$) whereas lens thicknesses did not show significant sex differences

Giving entirely analogous conclusions Table 6 7 presents the corresponding set of mean values for *emmetropic* eyes meaning the group of right eyes showing re fractive values from 0 to +0 9 D Axial length and vitreous length have now increased somewhat as compared with the mean values in the preceding table due to exclusion of the many rather short eyes with low hypermetropia

The conclusion on the whole must be that the ocular dimensional deficit of the

Table 6 7 *The same ocular parameters as in table 6 6* in 58 right eyes with *emmetropia* from the premature group and in 52 right eyes with *emme tropia* from the mature group
Mean values and standard deviations
Emmetropia here defined as refraction values from 0 to + 0 9 D

		Refrac- tion (D)	Axial length (mm)	*Depth of an terior cham- ber (mm)*	*Lens thick ness (mm)*	Vitre ous length *(mm)*	Cor neal curva ture radius (mm)
Right eyes with emmetropia	Prematures n = 58	+0 54 ±0.25	23 08 ±0 75	3 83 ±0 18	3 61 ±0 23	15 64 ±0 74	7 67 ±0 22
	Matures n = 52	+0 61 ±0.22	23 50 ±0 59	3 91 ±0 19	3 56 ±0 15	16 03 ±0 61	7 85 ±0 22
	Premature boys n = 28	+0 56 ±0 29	23 41 ±0 70	3 84 ±0 20	3 56 ±0 19	16 00 ±0 64	7 74 ±0 30
	Mature boys n = 29	+0 62 ±0 21	23 57 ±0 59	3 93 ±0 19	3 56 ±0 14	16 08 ±0 59	7 89 ±0 22
	Premature girls n = 30	0.52 ±0.22	22 77 ±0 67	3 81 ±0 18	3 65 ±0 26	15 30 ±0 67	7 61 ±0 28
	Mature girls n = 23	+0 59 ±0 23	23 41 ±0.59	3 89 ±0 19	3 55 ±0 17	15 97 ±0 64	7 81 ±0 22

prematures was a *general* feature of the group — and due not merely to those child ren who had the most deviating refractive values

(b) A supplementary analysis dealt with the eyes whose refractive values were most probably related to the prematurity as such *the eyes exhibiting pre school my opia.* Of the 27 eyes in this group 22 had been studied by ultrasound They were compared with the other myopic eyes measured by ultrasound viz premature (school myopic eyes, n = 21) and myopic eyes of mature children (n = 19) A few left eyes are included in the three groups of Table 6 8, for comparison the emme tropic eyes from Table 6 7 are added

Table 6 8 A comparison of *refractive value (in D) and axial length anterior chamber depth lens thickness and corneal curvature radius (in mm) in myopic eyes of the premature and mature group the former being subdivided according to the time of onset of the myopia*
Mean values and standard deviations
The table comprises the myopic eyes of the material in which axial ultrasound measurements were performed - In the last two columns the corresponding values of emmetropic eyes (from table 6 7) are added

	Premature eyes with pre school myopia n = 22	Premature eyes with school myopia" n = 21	Mature eyes with myopia n = 19	Premature right eyes with emmetropia n = 58	Mature right eyes with emmetropia n = 52
Refraction (Dioptres)	- 5 15 ± 3 76	- 1 0 ± 0 80	- 2 27 ± 1 57	+ 0 54 ± 0 25	+ 0 61 ± 0 22
Axial length (mm)	24 38 ± 1 48	23 90 ± 0 86	24 32 ± 0 92	23 08 ± 0 75	23 50 ± 0 59
Anterior chamber depth (mm)	3 77 ± 0 21	4 02 ± 0 31	3 95 ± 0 13	3 83 ± 0 18	3 91 ± 0 19
Lens thickness (mm)	3 79 ± 0 32	3 64 ± 0 25	3 58 ± 0 15	3 61 ± 0 23	3 56 ± 0 15
Corneal curvature radius (mm)	7 57 ± 0 30	7 70 ± 0 31	7 73 ± 0 27	7 67 ± 0 22	7 85 ± 0 22

Table 6 8 shows the mean values for refraction and refraction components Vitreous length is omitted as it varies parallel with axial length (and may incidentally be deduced from the listed data) Pre school myopes had the lowest mean refractive value and accordingly the lowest median The median values were –4 0 –0 75 and –2 5 D respectively for the three myopic groups in the table

The axial lengths of the myopic eyes considered together exceeded the emmetropic mean values However the pre-school myopes differed from the other two myopic groups in having an axial length shorter than expected from the refractive value Thus their mean axial length closely corresponded to that of the mature myopes – despite a definitely less marked myopia

Other striking features among the pre school myopes are the distinctly reduced corneal curvature radius the slightly reduced chamber depth and the somewhat thicker lens In other words the axial element in the myopia is essentially less pronounced than in the other myopic eyes Failing adaptation of the structures in the anterior eye segment seems to have had a decisive influence upon the refractive value in the pre school myopes

(c) The last refraction group comprises the children with *anisometropia* Of the 30 children having anisometropia exceeding one dioptre 17 could be subjected to ultrasonic measurement of both eyes This group is too small to permit relating oculometric differences to the degree of maturity at birth Therefore the oculometric side difference will merely be given in brief outline

The eyes having a lower (more negative) refractive value always had the longer axial length In the 17 children the anisometropia amounted to an average of 4.6 dioptres and the difference in axial length to 1 7 mm

All 30 anisometropes were subjected to keratometry on both sides One child had a side difference of 0 07 mm in corneal curvature radius – equivalent to a refractive difference of only 0 4 D In the remaining 29 the difference between the sides was ≤ 0 05 mm In other words side differences in corneal refractive power could not explain the anisometropias which were clearly of axial nature

Discussion

The annual growth rate of the eye is slow around the age of 10 Within the present material therefore one cannot expect a purely *chronological* deficit due to the 6 – 7 weeks that the prematures were behind the mature children at birth This view has previously been supported by the ocular measurements performed by Grignola & Rivara (1968) who reported full compensation within the first year of life for the oculometric deficit caused by premature birth

My findings in contradistinction have shown that *in prematures weighing less than 2000 g at birth ocular dimensions remain reduced also at longer sight* They show also that the slight reduction of ocular dimensions is a general feature in the group and that the optic components analysed did not show major deviations from the usual correlation pattern Lastly it may be emphasized from the previous chapter

that the refraction pattern among the prematures – when excluding the few pre school myopes – corresponds largely to that of the mature children

In other words the refractive values have not proved to be particularly influ enced by the dimensional ocular deficit of the prematures The latter is of the same order of magnitude as the difference between the two sexes and the analogy with the sex difference may be carried further still When assessed on the basis of ocu lometry and refractive values the premature eyes of the present material compare with the mature eyes like girls with boys eyes The correlation between the optic components ensures harmonious ' nan-ophthalmos" wihout any particular changes in refractive pattern The comparison with the sex difference is particularly striking if the few pre-school myopes are again omitted

From the oculometric data of the present material it cannot be established whet her the prematures as a group have delayed ocular development or a permanent deficit Analogy with the sex difference is complete only in the latter event This aspect will be discussed in more detail in the next chapter which introduces also extra-ocular growth parameters

Optical Calculations in Relation to Oculometric Differences

Sex differences in optic components have been analysed int al by Gernet (1964) who based his study on the mean values found in emmetropic eyes of both sexes He found the hypermetropizing effect of shorter axial length in women to be par tially compensated for by increased corneal refractive power (a shorter radius of curvature) but not sufficiently for the emmetropia actually present Gernet sought the explanation in increased lenticular refractive power in women and his calcula tions gave support to this theory However the evaluations suffer from the drawback that the calculations were based upon equations including axial length and corneal curvature radius, a false correlation is therefore inevitable

Thus the premises of some of the optical calculations may be questioned but making such calculations is in accordance with solid ophthalmological tradition Accordingly there are often two aspects of oculometric studies Submitting the data *and* assessing whether the data can be fitted in with existing knowledge concerning refraction factors or can give birth to new hypotheses

The premises may be divided into optical mathematical and empirical Corneal refractive power is an exponent of the former Presupposing a constant refractive index it is possible to calculate the refractive change entailed by a given change in the radius of curvature Within the physiological range a change of 0 1 mm in the radius of curvature corresponds to a refractive change in the range 0 5 – 0 7 dioptres In practice the equivalent changes are read direct from the keratometric scale

With regard to the association between variations in axial length and refractive value however the basis is predominantly empirical According to the classical rule of thumb (e g Karpe (1953) Brückner (1954) in ophthalmological textbooks) the ratio Δ axis Δ refraction is around 1 3 (the units mm and D) so that a one mm longer axis would mean a three dioptre change towards myopia This rule of thumb has

proved surprisingly viable in spite of the disparities substantiated in a number of oculometric publications

However, mathematical reflections may also be employed in this field Duke Elder (1970) for instance calculated the axial displacement of the image according to the dioptric value of lenses placed in the anterior focal plane of the eye On this basis the ratio between the two sets of changes could be stated as 0.39 mm/D or 2.57 D/mm These calculations however presuppose ceteris paribus but this demand is not fulfilled under *practical* conditions where correlations between the various optic components are operative A longer ocular axis is usually (Tscherning 1886 Sorsby et al 1957) associated with a longer corneal curvature radius and a relatively flatter lens (reduced lenticular refractive power) will also compensate for the myopizing effect of the longer axis The ratio between the two sets of changes must therefore in fact be expected to be less than the theoretically calculated 2 57 D/mm

Indeed the empirical results show considerable scatter So far two fundamentally different methods of calculation have been applied In some studies the assessment has been based exclusively upon two connected sets of mean values for axial length and refraction e g for *the* emmetropic and *the* myopic eye This is a coarse simplification which pays no heed to variations within the material In other studies the regression line has been calculated (on the basis of the method of least squares) and this is a more reasonable method The slope (b) then gives numerically the relationship between changes in the two parameters and the correlation coefficient (r) expresses the strength of the calculated association Between the quantities stated there is the relationship $b_{yx} \times b_{xy} = r^2$ In other words the regression coefficients differ according to which of the two variables has been selected as the dependent variable being exactly reciprocal only in the event of full correlation ($r = \pm 1\,0$) When r differs from $\pm 1\,0$ only part (r^2) of the variation in the two parameters is described by the calculated regression line The lower numerically the correlation coefficient the greater is the residual variation conditioned by factors *other* than the two parameters involved and then the difference between b_{yx} and $\frac{1}{b_{xy}}$ will increase

These factors are naturally of importance in assessing the data concerning the co[illegible] variation between refraction and axial length in different ophthalmological materials Using refraction as the independent variable (x) regression coefficients in the range −0.31 to −0 40 mm/D have often been reported (e g [illegible] 1966 Gernet 1969 Pallin 1969 Larsen 1971 [illegible] 1971) Using axial length as the independent variable Franceschetti et al (1968) found regression coefficients in the range −2 0 to −2 2 D/mm

Figs 6.3 and 6 4 set out the regression and correlation coefficients for the groups of the present material The findings for prematures and matures were [illegible] and −0.37 mm/D respectively and viewed the other way about [illegible] and [illegible] D/mm In other words there is a gap between the numerical expressions of co-vari[illegible] ation according to the choice of dependent variable The present r values also

indicate that a considerable residual variation must be ascribed to other factors not included in the regression equations

As a consequence of these reflections it is not possible to state for the association between changes in axial length and refraction a fixed numerical value valid *both* ways (directly or reciprocally) when attempting to estimate the size of one variable from that of the other Part of the explanation is the biological and methodological dispersion of data and another part the incomplete correlation between refraction and axial length The classical rule of thumb claiming a ratio of 3 D/mm (or reversely 0.33 mm/D) cannot be maintained Were a figure to be estimated for this ratio it would be according to my subjective estimate closer to 2 D/mm

On this basis I have not felt justified in carrying the classical optical calculations too far in the case of the present data Suffice it to be established that good agreement was found between the calculated and factual differences in the mean refractive values for the two groups The *emmetropic* mature eye had a longer axis than the *emmetropic* premature eye (Δ = 0 42 mm) and a greater corneal curvature radius (Δ = 0 18 mm) The two sets of changes tend optically to neutralize each other The same conclusion resulted when the mean values for *all* measured eyes of the two main groups were included – An estimate of lenticular refractive power (on the basis of simplified formulae suggested by van Alphen 1961 Leary et al 1963, and Gernet 1967) could not disclose a likelihood of 'lens myopia to explain the relative preponderance of myopes in the premature group

Special Considerations Applying to the Group of Premature Eyes with Pre-school Myopia

It was established above that the eyes of the *total* premature group follow largely the correlation pattern which applies to the optic components in the mature group and that the results are in keeping with those of a number of previous oculometric studies Thus the following *general* rules may be briefly recapitulated

Axial length is positively correlated to corneal curvature radius corneal size and chamber depth At increasing axial length the lens is often relatively flatter – Thus the myopizing effect of increased axial length is compensated for by a reduced refractive power of the cornea (Franceschetti & Gernet 1965) as well as lens (Franceschetti & Gernet 1965 François & Goes 1969 1973)

However the result for the total premature group does not rule out the presence of sub-groups differing from the norm outlined above In this connection attention must be focussed on the small fraction of *pre school myopic* eyes which represent the eyes which have been – at least hypothetically – injured by prematurity

The results within this group (mean values in Table 6 8) differ clearly from those of the total premature group Despite a greater axial length the pre school myopes had a shorter radius of corneal curvature flatter chambers and thicker lenses All three factors have acted towards myopia (instead of compensating as normally) and indeed the axial length is relatively short in relation to the degree of myopia

Let it be added that the transverse corneal diameter (analysed in the next

chapter) in the pre-school myopes showed a mean value of only 11 17 mm which is less than in the other refraction groups All considered the results for this group indicate that the trauma of prematurity has primarily affected the development of the *anterior* segment of the eye This fits well in with the impression of the total developmental pattern of the eye (cf next chapter) Judging by measurements of corneal curvature radius corneal transverse diameter, and axial length in relation to age the anterior segment of the eye has completed its development at an early juncture – far in advance of the posterior segment It is possible therefore that the structures of the anterior segment are more vulnerable to *early* noxae

The results for the pre school myopes can be naturally compared with studies elucidating the optic components in high myopia High myopia – often defined as having an arbitrary lower limit at –6 0 D – is interpreted by many authors as a latent or manifest pathological state In several materials such eyes have consequently been excluded in elucidating the "normal" co variation of the optic components

Indeed it applies to high myopia that the correlation pattern between the optic components may be altered Franceschetti & Gernet (1965) for instance, reported a greater corneal curvature in high than in low myopia Grieten & Weekers (1962) usually found a mutual negative correlation between chamber depth and refractive value but this applied only to eyes having refractive values down to –6 D at higher myopia there was no demonstrable correlation between chamber depth and eyeball dimensions

François & Goes (1973) reported that the corneal curvature radius chamber depth and lens thickness were of the same order of magnitude in the groups of myopes having refractive values higher and lower than –6 0 D This indirectly supports the findings of Grieten & Weekers (1962) The correlations which apply to the normal refraction range (including hypermetropia ametropia and low myopia) cannot be extended to comprise also the eyes with high myopia.

The present group of pre-school myopia is not characterized by truly high myopia The mean refraction as well as the median are below the borderline value of –6 0 D On the oculometric background outlined above however it is reasonable to consider the group as being "pathologically myopic – and prematurity the factor which has influenced the neonatal growth and early development of the eye

Summary and Conclusions

On comparison of the two groups of children aged about 10 years the eyes of the prematures were on an average significantly smaller than those of the mature children

When *all* eyes were included the differences in the most important optic components were about 0.3 mm for axial length and vitreous length and 0 18 mm for corneal curvature radius When the assessment was based *exclusively* on the emmetropic eyes the premature group exhibited a mean axial length of 23 1 mm and the mature group of 23 5 mm The corresponding corneal radii of curvature were 7 67 and 7 85 mm respectively

Antenor chamber depth was the same in the premature and mature group The boys chambers were 0 06 mm deeper than the girls ($p < 0 05$)

Lens thickness was significantly greater in the premature than in the mature children the difference being 0 05 mm ($p < 0 05$) The sex difference was not significant

Differences in axial vitreous lengths corresponded numerically quite accurately to the differences in axial eye lengths

The maturity difference in ocular dimensions was of approximately the same order of magnitude as the sex difference in the material Axial lengths in the girls were an average of 0.36 mm shorter than in the boys and the corneal curvature radius 0 11 mm shorter

Co variation of the optic components seemed unaffected by the prematurity The correlation pattern in the total premature group did not differ essentially from that in the mature group also not after grouping by sex In other words the eyes of the prematures were 'harmoniously smaller than the eyes of the matures In this respect too the maturity difference was analogous with the sex difference

The dimensional deficit in the prematures was a common feature of the group applying to the entire refraction range including the large middle groups around emmetropia

However the premature eyes with pre school myopia (myopia of prematurity?) differed oculometrically from the pattern of the total premature group In particular the development of the anterior eye segment seemed affected there being smaller and flatter corneae flatter chambers and thicker lenses Thus the axial element of pre-school myopia was less pronounced than in the residual fraction of myopic eyes in the material

The association between changes in optic components and in refraction changes is discussed The classical dogma that 1 mm Δ axis entails 3 dioptres Δ refraction cannot be maintained

CHAPTER 7

HEIGHT AND OTHER SOMATIC PARAMETERS

> – There are greater chances of encoun tering a long corneal radius in tall people and *especially in those having large heads* Nevertheless this influence is slight since the variation of the mean for the corneal radius as related to various levels of body height and skull circumference is far less than the differences which may be found in people of the same height or having the same circumference of the skull
>
> (M Tscherning 1886)

Introduction

Postnatally the eye shows approximately the same growth pattern as the brain Both increase 3 or 4 times in weight from birth to adult age and the growth occurs pre dominantly during the first years of life (Weiss 1897 Wolff 1948 Keeney 1951 Sorsby et al 1961) For comparison it may be mentioned that the adult body weight is about 20 times the birth weight and that growth estimated from weight and height is fairly even during the first 14 – 18 years

In the eye growth is completed first in the anterior segment Only negligible changes in corneal diameter and curvature seem to occur after the age of 2 years (Keeney 1951 Sorsby et al 1961) while axial length still increases a little – indi cating a continued but slight enlargement of the posterior segment

Thus the growth pattern of the eye differs completely from the general somatic growth pattern There is no definite relationship to sexual development except for the chronological coincidence in the fraction of adolescents who develop juvenile *myopia With this exception there is no evidence of an ocular* growth phase in con nection with puberty On the contrary most eyes appear to have attained their ultimate size before that time (Sorsby et al 1961 Larsen 1971)

Now the question arises whether the *ocular* dimensional deficit demonstrated in the previous chapter is an isolated phenomenon or whether the prematures of the present material also exhibited other somatic signs of inhibited development To answer this question measurements of body height, circumference of skull and interpupillary distance were analysed The results will be reported below together with those of measuring ocular protrusion and transverse diameter of the cornea

Present Results

The *measuring methods* were described in Chapter 3 Unless otherwise stated the significance calculations were parametric (t test) as we are dealing with parameters of approximately normal distribution

Table 7 1 *Mean age and height* with standard deviations in the premature and mature group (top) and in subdivisions by sex (bottom) The third column shows the *mean percentile height* in the same groups (after conversion of each measured height in cm to percentile height reference values published by Stuart & Stevenson 1959 see also text)

	Mean age (years) at examination ± SD	Mean height (in cm) ± SD	Mean percentile height
Prematures n = 302	10 27 ±0 94	137 2 ±8 1	32 9
Matures n = 237	10 28 ±0 93	140 9 ±7 9	48 9
Premature boys n = 150	10 36 ±0 90	137 9 ±8 0	32 5
Mature boys n = 113	10 29 ±0 95	141 3 ±7 5	50 5
Premature girls n = 152	10 18 ±0 98	136 6 ±8 3	33 3
Mature girls n = 124	10 27 ±0 92	140 6 ±8 3	47 6

Height and Age at Ophthalmological Examination

Table 7 1 lists the mean body height in the premature and mature groups of the material also sub-divided by sex The table includes the mean age in the groups as even slight age differences have a marked influence upon the assessment of height

The mean annual increment in height may be considered 5–6 cm at that age The heights given in the table were corrected accordingly prior to the significance calculations After correction for age of the groups compared two and two the following differences were observed

Premature boys	$<$	mature boys	$\Delta = 3\ 8$ cm	($p < 0\ 01$)
Premature girls	$<$	mature girls,	$\Delta = 3\ 5$ cm	($p < 0\ 01$)
Premature children	$<$	mature children	$\Delta = 3\ 7$ cm	($p < 0\ 01$)
Premature girls	$<$	premature boys	$\Delta = 0\ 6$ cm	(not significant)
Mature girls	$<$	mature boys	$\Delta = 0\ 6$ cm	(not significant)

It may be rightly claimed that to do full justice to the premature group the age correction should be from the time of conception – not from the date of birth Such further correction reduced the maturity difference by about 1 cm but the difference between prematures and matures remained statistically significant

Percentile Height

Inhibition of growth may also manifest itself in a relatively larger number of children who are small for their age To evaluate this further the author introduced the concept *percentile height* to indicate height in relation to age, stated in relation to a reference material To this end I used Stuart & Stevenson s (1959) growth norms which have been tabulated as a number of percentiles – P_3 P_{10} P_{25} P_{50} P_{75} P_{90} and P_{97} – at different ages during growth Thus the percentile height 50 signifies the median in the reference material A percentile height of e g 25 in a boy means that 25% of boys of exactly the same age were shorter and 75% taller

On the basis of the percentile value in the reference material a computer programme was worked out *for calculating percentile height by linear interpolation* Therefore the height of every child in the present material could be stated on the basis of age and sex as percentile height – The last column of Table 7 1 shows that the mean percentile height of the mature children was close to the median P_{50} In the prematures the mean percentile height was P_{33}

The distribution of the percentile heights in the material is shown in Table 7 2 sub-divided according to the seven percentiles stated above The percentage distribution of the mature children was in accurate conformity with the reference material In the prematures there was a distinct shift towards lower percentile values On the basis of the cumulated frequencies (Kolmogorov-Smirnov two sample test) this shift

Table 7 2 *Distribution* (in per cent) *of percentile heights* on the eight percentile classes of the reference material for the premature and mature group (The "ideal" distribution in the last column)

Height classes according to the percentiles published by Stuart & Stevenson 1959		Prematures n = 302	Matures n = 237	Reference distribution (by definition)
	P_0 - P_3	11 8%	3 8%	3%
	P_3 P_{10}	16 9%	8 6%	7%
	P_{10} - P_{25}	23 2%	11 0%	15%
	P_{25} P_{50}	16 9%	26 2%	25%
	P_{50} - P_{75}	19.5%	23 6%	25%
	P_{75} - P_{90}	6.3%	18 1%	15%
	P_{90} P_{97}	4 0%	6 3%	7%
	P_{97} - P_{100}	1 4%	2 4%	3%

proved to be significant ($p < 0\ 01$) in relation to the mature group as well as the reference material

Within the premature group there was a significantly positive correlation be tween birth weight and percentile height ($r = 0\ 19 \neq 0$ with $p < 0\ 01$) and thus applied especially to the boys ($r = 0\ 25$) In the girls however the correlation was not sig nificant at the 0 05 level ($r = 0\ 14$)

Within the group of prematures weighing at birth $\leqslant$ 1500 g 36% of the heights were below the 10-percentile and the mean percentile height was 27 4 The fraction of prematures with birth weights $>$ 1750 g had 24% below P_{10} 47% below P_{25} and a mean value of 37 5 Thus this fraction of prematures was closer to the refer ence material but still showed a significant shift towards lower values

The small group of prematures with pre-school myopia was predominated by children of the birth weight class $\leqslant$ 1500 g and showed similar results The mean percentile height was 28.3 for the 15 premature children with pre school myopia

Percentile Height in Relation to Maternal Height

Body height is to a marked extent inherited Tall parents usually have children who are tall for their age and the reverse applies to small parents and their children There

Table 7.3 *Height (in cm) of mothers* of infants in the premature and mature group of the material Frequencies (in per cent) of different height groups n = number of children for whom the maternal height was known (data from the basic material)

		Mothers of prematures n = 290	Mothers of matures n = 236
Maternal height	Less than 150 cm	1 4%	0 8%
	150 154 cm	10 0%	5 1%
	155 159 cm	22 1%	20 8%
	160 169 cm	53 8%	57.2%
	170 cm and taller	12 7%	16 1%

Table 7 4 *Mean percentile height of children* in the premature and mature group *subdivided by maternal height* n = number in each subgroup

		Mean percentile height of children of	
		the premature group n = 290	the mature group n = 236
Maternal height	Less than 150 cm	17 5 n = 4	17 5 n = 2
	150-154 cm	13 3 n = 29	22 4 n = 12
	155 159 cm	23 7 n = 64	34 6 n = 49
	160 169 cm	36 3 n = 156	52 0 n = 135
	170 cm and taller	51 6 n = 37	69 3 n = 38

is accordingly the theoretical possibility that the premature children were smaller than the mature ones merely because their parents were small so that it would not be fair to attribute the deficit in height to the trauma of prematurity" This is elucidated in more detail in Table 7.3 which gives the distribution of maternal height

in the two main groups Paternal height was known only sporadically and could not be included in the table

From Table 7.3 it may be seen that the distributions on the various height groups were approximately the same for both groups of mothers ($p > 0.05$ Kolmogorov-Smirnov) This assessment could not be based on parametric tests (employing mean values and S D) as maternal height had been coded on the punch cards of the *basic* material only in the height classes given in Tables 7.3 and 7 4 not in accurate values

The influence of maternal height upon the child s percentile height is demonstrated in Table 7 4 Small mothers had on the whole children who were small for their age tall mothers taller children and this applied to the premature as well as the mature group Thus the mean percentile height of the children increased with the maternal height *However the difference between the level in the prematures and in* the matures was systematically present In other words the height *deficit* of the prematures was found to bear no definite relation to maternal height

Table 7.5 *Mean values and standard deviations of skull circumference interpupillary distance exophthalmometry value (right eye) and transverse corneal diameter* (right eye) for the premature and mature group (top) and in sub-divisions by sex (bottom)

	Skull circumference (cm) Mean value ± SD n = number of children	Interpupillary distance (mm) Mean value ± SD n = number of children	Exophthalmometry value (Luedde mm) Mean value ± SD n = number of right eyes	Transverse corneal diameter (mm) Mean value ± SD n = number of right eyes
Prematures	52 6 ± 1 69 n = 302	57 7 ± 3 12 n = 302	13 4 ± 1 72 n = 279	11 39 ± 0 48 n = 302
Matures	53 5 ± 1 58 n = 237	58 3 ± 2 96 n = 237	14 2 ± 1 87 n = 197	11 54 ± 0 45 n = 237
Premature boys	53 0 ± 1 60 n = 150	58 2 ± 3 11 n = 150	13 6 ± 1 78 n = 139	11 45 ± 0 47 n = 150
Mature boys	54 1 ± 1 48 n = 113	58 4 ± 2 91 n = 113	14 3 ± 1 99 n = 95	11 63 ± 0 43 n = 113
Premature girls	52 2 ± 1 69 n = 152	57 2 ± 3 06 n = 152	13 2 ± 1 64 n = 140	11 34 ± 0 47 n = 152
Mature girls	53 0 ± 1 53 n = 124	58 2 ± 3 01 n = 124	14 0 ± 1 74 n = 102	11 46 ± 0 46 n = 124

Circumference of Skull Interpupillary Distance Ocular Protrusion and Transverse Diameter of Cornea

The results are given in Table 7.5

Circumference of Skull

Range Premature children 47.5 – 59 cm
Mature children 48 0 – 60 cm

The following differences between the groups are shown in Table 7.5 all significant ($p < 0\ 01$)

Premature boys	<	mature boys	$\Delta = 1\ 11$ cm
Premature girls	<	mature girls,	$\Delta = 0\ 81$ cm
Premature children	<	mature children	$\Delta = 0\ 95$ cm
Premature girls	<	premature boys	$\Delta = 0\ 78$ cm
Mature girls	<	mature boys,	$\Delta = 1\ 09$ cm
Girls	<	boys	$\Delta = 0\ 93$ cm

In other words the circumference of the skull was significantly smaller in the premature than in the mature children The mean difference of almost 1 cm was in the same range as the sex difference in the material

Interpupillary Distance

Range Premature children 48 – 68 mm
Mature children 52 – 65 mm

The differences between the groups are again apparent from Table 7.5 Interpupillary distance in the prematures was significantly shorter (at the 0 05 level) than in the matures The difference averaging 0 6 mm was in the same range as the sex difference in the material

Ocular Protrusion

In nearly all children having exophthalmometry the reading was the same for the right and left eye Only 3% exhibited a side difference exceeding 1 mm and the correlation coefficient for right and left eyes was high ($r = 0\ 96$) Therefore the significance calculations were based solely upon the right-eye readings The protrusion of the eye in relation to the anterior lateral orbital margin was 0.8 mm less in the premature than in the mature children (cf Table 7.5) This difference is significant at the 0 01 level The maturity difference exceeded the sex difference (0.32 mm) which was not significant for this parameter

Transverse Corneal Diameter

Range   Premature children   9 0 – 12 5 mm
         Mature children   10 5 – 12 75 mm

The mean value in the premature group was significantly below that in the mature group (p < 0 01) The maturity difference averaging 0 15 mm was in the same range as the sex difference in the material (0 14 mm, significant at the 0 01 level) There was a high correlation between the right and left eye (r = 0 99)

Correlation Between the Various Growth Parameters

Tables 7 6 and 7 7 give for the premature and the mature children the degree of correlation between birth weight and the three most accurately measurable of the extraocular growth parameters analysed body height circumference of skull, and interpupillary distance At this site height is entered – like the other growth parameters – by the direct values i e not by the percentile height whose correlation to birth weight has been elucidated already The correlation matrix also comprises three ocular parameters axial length, corneal curvature radius and refractive value

Table 7 6 *Correlation matrix with correlation coefficients (r) between birth weight height skull circumference interpupillary distance and three ocular parameters* axial length corneal radius and refraction value as measured on 191 children of the *premature group*
Correlation coefficients are shown only when differing from zero at *significance levels 0 01 in bold types (r>0 186) and 0 05 fine types* (r>0 142)

Height	Skull circum ference	Inter pupillary distance	Ocular axial length	Corneal radius	Re-fraction	
19	16			18		Birth weight
	.46	43	29	22		Height
		45	.33	.33		Skull circum-ference
			25	25		Interpupillary distance
				56	61	Ocular axial length
						Corneal radius

Table 7 7 *Correlation matrix for the same parameters as in table 7 6* for 159 children of *the mature group*

Correlation coefficients are shown only when differing from zero at significance levels 0 01 bold types (r>0 204) and 0 05 in fine types (r>0 156)

Height	Skull circum ference	Inter pupillary distance	Ocular axial length	Corneal radius	Re-fraction	
						Birth weight
	.29	41	19			Height
		.35	21	17		Skull circum ference
						Interpupillary distance
				.37	62	Ocular axial length
					.20	Corneal radius

To make the two tables more perspicuous those correlation coefficients which did not differ significantly from 0 were omitted The analysis includes 191 premature and 159 mature children whose right eyes were measured by ultrasound

It will be noted that *birth weight* in the premature group was correlated though weakly to height circumference of skull and corneal radius whereas the mature children showed no significant correlations between birth weight and the other parameters Indeed this was not to be expected seeing that the mature group was selected as a homogeneous birth weight group

The *three extraocular growth parameters* (height circumference of skull and interpupillary distance) were in mutual positive correlation in both groups Among the prematures there was also a correlation (though weak) to the two refractive components (axial length and corneal radius) These correlations in the mature children were either even weaker or not significant

Correlation of *refraction* to axial length has been discussed in more detail in the preceding chapter Multiple regression analysis confirmed that the influence of extraocular growth parameters on refraction is entirely subordinate to the far closer associations especially with axial length and corneal curvature radius

Discussion

Let it be emphasized first that the present material homogeneous with regard to age does not permit deductions concerning the *growth rate* as such This requires either repeated measurements of the same children at intervals of years or comparison of mean values in age groups differing more than those of the present material

The word *growth* has nevertheless been used in various connections in the present chapter, in this context it refers to the degree of development at the given age judging by the size of the growth parameters measured Thus, a *growth deficit of prematurity* simply signifies that a given parameter is below that in mature children

The discussion will be divided into the following six items Influence of prematurity upon the growth parameters measured – Permanent or temporary growth deficit in prematures – Prematurity and ocular protrusion – Association between the growth parameters measured and refraction – Influence of social factors – Aetiological considerations

Influence of Prematurity Upon the Growth Parameters Measured

Where *body height* is concerned the children of the premature group had *not* at the age of 10 years caught up with the mature children of the same age The mean deficit was 3 7 cm The growth inhibition or delay of the prematures could not be explained merely by differences in conception age or maternal height Reduced height in premature children has previously been reported by int al Blegen 1953, Gedda 1962 Biering-Sørensen et al 1962 McLaughlan 1963 Drillien 1964 Harper & Wiener 1965 Janus Kukulska & Lis 1966 Lubchenco 1968

Height in the mature children of the material corresponded accurately to the age norms based upon measurements of American children of predominantly North West European descent The values of the present study were also consistent with the most recent Scandinavian normal material (Karlberg 1973)

The sex difference averaged only 0 6 cm, the boys being taller This corresponds to the general experience that the earlier onset of the juvenile growth spurt in girls has almost equalized the lead of the boys up till then

Circumference of the skull was also significantly smaller in prematures than in the mature children This accords with previous measurements by Brander (1940) *Growth curves for cranial circumference (e g Sundal 1962) show in general a marked* increment of 11–12 cm during the first year of life In the second year it increases by about 2 cm and in the third year by about 1 cm After the age of 6 years the mean annual increment is less than 0 5 cm and the final adult value is attained by the age of 12 – 15 years Thus the growth of the skull follows the growth pattern of the brain

The same applies with modifications to the *orbit* According to Sachsenweger (1971) the orbit attains its ultimate size already at the age of 10 – 12 years i e considerably earlier than body height On this item however there is not entire agreement Sachsenweger (1971) supported his view int al upon Doden & Pro-

tonotanos (1960) measurements of the *interpupillary distance* in children in the age range 4 to 9 years Older children and adolescents are not mentioned but these categories have been elucidated in studies quoted by Eisler (1930) showing mean values of 57 60 and 63 mm for 10-year-olds 15 year-olds and adolescents respectively This is also in keeping with Keeney s (1951) assessment Thus we have evidence that the interpupillary distance does not merely follow the cerebral growth pattern but that it also – like the facial bones – takes part in the puberal growth phase

In contradistinction the growth of the cornea has been completed at a very early juncture and for this reason the *transverse corneal diameter* was included in the analysis The object was to enter a parameter which could be considered to have completed its growth by the age of 10 years

The *interpupillary distance* as well as the *transverse corneal diameter* measured significantly less in the premature than in the mature group of the present material To my knowledge these two items have not been analysed in previous premature samples

Permanent or Temporary Growth Deficit in Prematures

As the total result of the measurements the prematures showed a significant growth deficit applying not only to ocular dimensions (axial length vitreous length corneal radius of curvature and transverse corneal diameter) but also to body height circumference of skull and interpupillary distance On the basis of the present findings it cannot be decided whether there is a permanent deficit or whether the delayed prematures may compensate later This question can only be answered by a regular follow up study However several factors indicate a permanent deficit (1) At the age of 9 – 11 years the growth of the brain is being completed further the transverse diameter of the cornea has reached its adult size – and in this respect at least the deficit is permanent (2) Where body height is concerned Alm (1953) has previously found a group of full-grown prematures to be significantly shorter than a mature control group

Prematurity and Ocular Protrusion

Exophthalmometry revealed in the premature children lower mean values than in the mature ones In fact this measurement expresses a relative value stating the protrusion of the eye as the distance between the lateral orbital margin and the corneal vertex Therefore it is difficult to involve exophthalmometry direct in the growth reflections

However this measurement was included here to elucidate another item Among the classical neonatal stigmas of prematurity protruding eyes have been pointed out (Ylppo 1919) and several authors have maintained that this feature is present also at longer sight Brander (1940) in a follow up study of 379 premature children of

school age found 'protrusio bulborum in 30% – without further defining this concept The most frequently affected group was that of a birth weight below 2000 g in which 40% had this sign There was no control group but Brander quoted Hess Mohr & Bartelme (1934) as having found 11 6% with protrusio bulborum among 250 prematures as compared with only 6 4% of full term control children recruited from among the prematures siblings However the difference between these two frequencies is not statistically significant (χ^2 test) Thus the view rests on a weak foundation and could not be confirmed in the present study On the contrary the prematures showed less protrusion of the eyes than the matures

Association Between the Growth Parameters Measured and Refraction

Tables 7 6 and 7 7 demonstrate the relationship between growth (expressed by various parameters at a given age) and refraction The background is the often advanced view on an association between a high growth rate (degree of somatic development) and the appearance of myopia Thus groups of myopes have often proved of a greater mean height than groups of emmetropic and hypermetropic individuals, a number of these studies were reviewed by Goldschmidt (1966) Gar diner (1954) considered another developmental criterion the onset of the menarche which he found to occur significantly earlier in myopic than in non myopic girls However Sorsby *et al* (1961) could not confirm the theory of a relationship be tween a high growth rate and the development of myopia Holst & Tjåland (1962) even made the reverse finding in Norwegian school children viz that myopic child ren were shorter than non myopic

In the present material it was *not* possible to demonstrate a significant correla tion between height and refractive value This may be interpreted as the resultant of two opposite correlations since height (and the other extraocular growth parameters) – at least in the prematures – proved to be correlated to axial length as well as corneal radius However the mutual correlation between these ocular para meters tends to neutralize the refractive change which would be induced by vari ation in one of them

Thus the present material did *not* at the age studied viz about 10 years con firm the hypothesis of an association between juvenile growth rate – expressed here by the size of the analysed growth parameters – and development of myopia

Influence of Social Factors

Goldschmidt (1966) emphasized the role of social classification in assessing body height In his study myopic conscripts were an average of 1 6 cm taller than non myopic conscripts However this difference in height was eliminated when keeping within the same social/occupational stratum Thus it is well known that the fre quency of myopia is particularly high among students who are also somewhat taller

than the general population (and who have been recruited predominantly from homes having an academic tradition)

Here only a rough estimate of the possible influence of social classification upon the above results As regards refraction the premature as well as mature group showed a lower mean refractive value in the socially best situated fraction of the material (classes I – III inclusive cf p 30) as compared with the lowest social classes (IV + V) Thus the tendency was into the expected direction but the difference of 0.3 D is not statistically significant at the 0 05 level Regarding the relationship between height and social class the percentile heights were significantly shorter in the lowest classes but this applied only to mature children

In other words the influence of social factors could be traced in the present material but they have hardly had any effect upon the conclusions concerning the growth deficit of the prematures there being no significant social skewness between the premature and mature group

Aetiological Considerations

On the basis of the findings in the present material it is not reasonable to draw far reaching aetiological conclusions especially when considering a certain interplay between several of the parameters involved whereas other possible parameters have not been elucidated at all

However there is reason to point out two factors which directly and indirectly indicate the role of prematurity The indirect evidence is the relationship between social class and percentile height which was present only in the mature group In the case of the prematures this association is probably masked by what primarily distinguished them from the matures the low birth weight – The more direct evidence is the larger number of significant correlation coefficients in the correlation matrix of the prematures (Table 7 6) as compared with the mature children s (Table 7 7) It must be assumed that – when taking the values of the mature group as the norm – it is the prematurity (= birth weight) which has entailed the increased number of significant correlations by virtue of its influence upon the *total* somatic development The greater the prematurity the more marked the size deficit ocular and extraocular

Apart from the birth weight it has not been possible to demonstrate on the basis of the data of the basic material any pre or perinatal risk factors exerting a special influence upon the child s growth Thus supports – again indirectly – the view that it is the trauma of prematurity itself which is reflected in the size of the various growth parameters and their interplay

Summary and Conclusions

Parallel with the *ocular* dimensional deficit in prematures there was an effect also upon other parameters The mean values for body height circumference of skull

and interpupillary distance were significantly lower in the premature than in the mature group

A prematurity *deficit was demonstrable also for the size of the transverse cor* neal diameter This parameter is considered to have completed its growth long before the age studied viz 10 years This suggests a *permanent* prematurity deficit – not merely delayed development

There was some association between the various growth parameters analysed (height circumference of skull interpupillary distance and transverse corneal dia meter) but not with the refractive value

Two generally held theses were tested on the basis of the present data That myopes are recruited predominantly among children who are tall for their age and that premature children – as a reminiscence from the neonatal period – exhibit increased ocular protrusion Neither thesis could be supported and the latter was rejected

Within the premature group there were no special hereditary or exogenous *factors to explain the general deficit in size Therefore it is believed to be due to* the trauma of prematurity itself

CHAPTER 8

VISUAL ACUITY

As a rule the visual status of an individual is expressed clinically by the *visual acuity and the visual field* These are the main parameters used for assessing whether a patient is able to fulfill everyday demands on vision in the usual binocular situation Of course it is impossible to draw sharp limits between a so-called normal status and a real visual handicap in each case personal as well as social factors have to be taken into consideration

In the present study *visual field* examination was carried out only when indicated by the history and clinical findings suffice it here to refer to Cases 28 and 29 (Appendix) On the other hand assessment of *visual acuity* was performed consistently and the results will be reported below

Initially a brief review of literature dealing mainly with two items (a) The physiological development of visual acuity i e age *norms* for children and adolescents (b) The occurrence of *abnormal vision* in the population and in risk groups — e g in children of a low birth weight

Previous Findings

Physiological Development of Visual Acuity

Central vision is generally considered poor neonatally A few weeks maybe months will pass before fixation and following movements have become steady At an estimate the visual acuity of 6/60 has been achieved before the end of the first year and from the age of 4 – 6 years most children show 6/6 (Lyle & Bridgeman 1959 Sobansky et al 1962 Andree 1964 Ffooks 1969 Harcourt 1969 Lippmann 1969 Streiff 1969 and others)

During the first years of life it is difficult to determine visual acuity Evaluations are best done by grading the stimuli by which optokinetic nystagmus may be evoked It is observed whether this reflex mechanism can be triggered by the given stimulus but the actual visual angles cannot be converted direct to the usual Snellen fractions (Lewkonia 1969) So far it has not been definitely demonstrated whether it is the

minimum separabile or the *minimum visibile* which is being determined (Reinicke & Cogan 1958)

Dayton et al (1964) established that at least some neonates respond by optokinetic nystagmus to stimuli that subtend angles equivalating with Snellen values exceeding 6/60 Recently Catford & Oliver (1973) have reported essentially higher physiological levels than generally assumed for the first years of life They found a visual acuity corresponding to 6/18 at the age of 5 months 6/12 at 18 months 6/9 at 2 years and the "adult acuity 6/6 as early as the age of 3 years However their results are based upon a method whose principle differs to some extent from those utilizing true optokinetic nystagmus They did *not* aim at inducing nystagmus by the aid of the even continued passage of uniform stimuli but at making the infant follow an object (a round black dot) which itself describes horizontal oscillating nystagmus (slow phase forward/ rapid backward) 6/6 was recorded when a follow nystagmus could be induced by means of the smallest object at the given distance (60 cm) subtending a visual angle of 5 (at the nodal point of the eye) This too marks a difference from the usual Snellen symbol whose *details* are perceived at the visual angle of only 1

The results of testing visual acuity apparently depend highly upon method and test conditions Optokinetic nystagmus represents an experimental situation remote from everyday visual conditions Indeed it is generally accepted that in the more common test situation with a chart 6/6 cannot be expected as early as claimed by Catford & Oliver (1973)

In most cases it is not possible until the age of 3–4 years to carry out subjective visual testing by charts worked out according to the principles applying to Snellen s test type chart There is invariably a great dispersion around the mean curves of young children (cf Oppel 1964) Part of this dispersion is presumably physiological at the receptor level but the results are affected also by mental and psychological factors A more homogeneous performance level is not attained until school age

Norms should be fixed on the basis of representative random samples of children School materials are well suited except that they exclude the fraction of children who cannot be taught within the framework of normal schools because of various handicaps However the primary object of the visual testing done by the school medical officers is to single out the children with poorest vision and refer them to an ophthalmologist This means a fairly rough sorting of the children Hypermetropic and astigmatic children often do quite well in the visual test which on the other *hand is fairly certain to catch the small fraction of myopes Indeed* ophthalmological studies based on school material have been concerned predominantly with myopes (e g Holm 1926 Knudtzon 1941 Johansen 1950 Goldschmidt 1968) As to the visual acuity in the remaining children we merely know that without correction it has been 6/9 or better

Holst & Tjåland (1962) studying 9 10 year-old Norwegian school children (n = 6,333) found a visual acuity of 6/6 in 87% After correction only 3% were unable to achieve 6/6 binocular vision, 0 05% were weaksighted (≤ 6/24) Engbæk (1970) reported visual defects in almost 8% of children in the first form (n = 1 764 age 7 years) but when subsequently examined by an ophthalmologist only 13 of the

children could not achieve more than 6/18 (0 7%) Oster & Kjærgaard (1964) found a need of ophthalmological assessment in 30% of Danish school children (n = 2 229 age 6 – 17 years) and 14% were supplied with spectacles but the exact visual acu ities were not specified – Similar assessments have been published from other countries e g by Doden & Protonotanos (1960) Zilberman (1963) Abeloos (1970) and Parks (1972)

From the above it is apparent merely that the great majority of children at school age may be made to see 6/6 but it is not possible to deduce age related norms of visual acuity Several authors have tried to establish such norms Slataper (1950) supplemented his own findings with Brown s (1938) figures for *monocular* visual acuity According to these findings a level corresponding to 6/6 was attained at an average age of 10 – 12 years Oppel (1964) determining binocular visual acuity in children aged 2 – 6 years found a steady increase from a mean value of less than 6/12 at 2 years of age up to 6/6 at 5 years However these materials were not truly representative their subject was the normal eye and children with major degrees of ametropia amblyopia and heterotropia were excluded In connection with a trial of a vision testing apparatus Marquardt & Weber-Cause (1968) reported the mean visual performance of young children However their material was not large (a total of 86 children in the reasonably well represented age range 4 – 6 years) Furthermore the criteria of selection were not mentioned and visual acuities above 6/6 not specified

Abnormal Visual Acuities Among Children

To the above – numerically low – occurrence of impaired vision in various school materials I can add Påske & Andersen s (1970) findings among 18 000 school children in a Danish county They reported 0 11% to be weaksighted (visual acuity 6/18 or poorer) – just the number that might be expected in countries of a cultural and hygienic standard like Denmark s

With particular regard to premature children there have been no actual epi demiological studies It has been stated in a review by Harper & Wiener (1965) that "in general low birth weight children have a higher incidence of visual defects than do mature infants but data on this are complicated by the high incidence of retro lental fibroplasia from the early fortie s until about 1953"

However Eames (1946) and Castren s (1955) groups of prematures were not loaded by retrolental fibroplasia both materials were predominated by children of school age Among 155 prematures Eames found 42% to have visual acuity corre sponding to 6/9 or less against only 18% in the control group of full term children (n = 439) but it is not stated whether this was the uncorrected vision or the optimally obtainable (with glasses) Castren reported amblyopia – defined as an optimally corrected binocular vision lower than 0 4 – in 4% of the premature group (n = 480) and in 1 4% of the mature children (n = 217) but visual acuity findings were not further specified

The following two materials comprised groups of children whose birth weight

had been a maximum of 4 lbs (1815 g), both included children with as well as without retrolental fibroplasia Zacharias et al (1962) followed 237 children Among the eyes subjected to determination of uncorrected visual acuity 52% had 6/9 or better whereas 14% had $\leqslant$ 6/24 With correction there was a marked shift towards higher visual acuity 80% of the eyes achieving 6/9 or better and the incidence of acuities $\leqslant$ 6/24 being reduced by half McDonald s (1962 and 1967) material com prised 1 081 premature children of school age 55 (5%) were blind or suffering from severe visual defects, retrolental fibroplasia was responsible in 40 of the 55

In Moller s (1970) study of ocular changes in prematures (n = 640 age 3 – 4 years) no mention was made of visual acuity

It is not possible to draw more concise conclusions from the somewhat inho mogeneous series of prematures quoted above Only it seems that a definitely higher frequency of visual defects must be expected in premature than in mature children

Present Findings

In all children the visual acuity was determined in the binocular situation as well as for each eye separately They were offered glasses in a test frame initially as well as at the final assessment following retinoscopy

Vision was tested in the usual eye clinic set up with a well illuminated Snellen chart at a distance of 6 metres In a few cases with severe visual defects the distance had to be reduced Children who were not quite familiar with the alphabet were tested with numbers illiterate E s or a picture chart (Østerberg) all based on Snel len s principle

A correct set-up was of course difficult in the small fraction of prematures who were examined in the homes However it was always possible to obtain the correct distance and a good illumination of the chart and the set up could be checked to some extent by comparison with my own visual performance

According to custom the optimal visual acuity was given by the number of correctly stated lines and symbols on the chart On the basis of an early pilot study the material could be expected to include only a small number of children with marked visual impairment Therefore it was endeavoured to carry out the finest differentiation of the results within the upper part of the visual performance scale In the punch-card analysis the findings for the right left and for both eyes were classified as follows

(1) 6/4 5 (2) $>$ 6/6 (3) $\leqslant$ 6/6 (4) $\geqslant$ 6/9 (5) 6/12 – 6/18 (6) 6/24 – 6/60, (7) 3/60 – perception of light and (8) no perception of light

The sections below report first the corrected binocular (social) vision and thereafter the corrected monocular visual acuity for the 302 premature and 237 mature children of the material

Table 8 1 gives the distribution of the various binocular visual acuity findings 99% of the prematures and all mature children had – socially speaking – good vision There was no child in the actual weak-sighted group (6/24 – 6/60) whereas 1% of the prematures had to be classified as blind These were three children of the birth weight group ⩽ 1500 g two of them had retrolental fibroplasia (Cases 1 and 2) and one had congenital cataract (Case 31 cf Appendix)

Table 8 1 *Corrected binocular Snellen visual acuity* for distance in the premature and mature group (left) and in the premature group subdivided by the birth weight limit 1500 g (right)
Frequencies in per cent

	Prematures n = 302	Matures n = 237	Prematures of birth weights <1500 g n = 90	Prematures of birth weights >1500 g n = 212
6/4 5	28 0%	46 4%	17 8%	32 6%
>6/6	31 6%	38 8%	28 9%	33 0%
≦6/6	30 3%	11 8%	33.3%	28 3%
≧6/9	7 6%	3 0%	11 1%	6 1%
6/12-6/18	1 6%		5 6%	
6/24-6/60				
3/60 to light perception	0 7%		2 2%	
No light perception	0 3%		1 1%	

Visual acuity above 6/6 was found significantly more often ($p < 0\ 01$ χ^2 test) in the mature (85 2%) than in the premature group (59 6%) The birth weight group ⩽ 1500 g (n = 90) made a significantly poorer score than the remainder of the premature group (n = 212) 46 7% and 65 6% respectively having a visual acuity above 6/6

Fig 8 1 sets out graphically the binocular visual acuity findings The cumulated frequency curve is appreciably lower for the premature than for the mature group According to the Kolmogorov-Smirnov non parametric two-sample test the difference between the two curves is significant at the 0 01 level

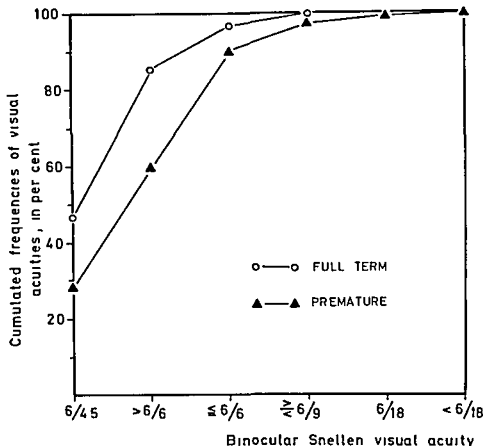


Figure 8 1 *Binocular visual acuity* (with best correction for distance) of children in the premature and mature group
Cumulated frequencies in per cent

Fig 8 2 in the same way illustrates the findings for the children of the premature group in three fractions divided by birth weights 1500 and 1750 g The curve representing the birth weight group ≤ 1500 g is situated clearly below those of the other two fractions which are almost identical The course of the ≤ 1500 g curve is significantly lower in relation to that of the 1501 – 1750 g group ($p < 0.01$) as well as to that of the group comprising all prematures weighing more than 1500 g ($p < 0.025$) However the difference from the fraction of prematures weighing > 1750 g is not significant (all assessed by the Kolmogorov-Smirnov test)

In other words the visual acuity findings in the premature group are loaded to a marked extent by the ≤ 1500 g group but this fraction is not solely reponsible for the poorer total score in the premature group The total result for prematures

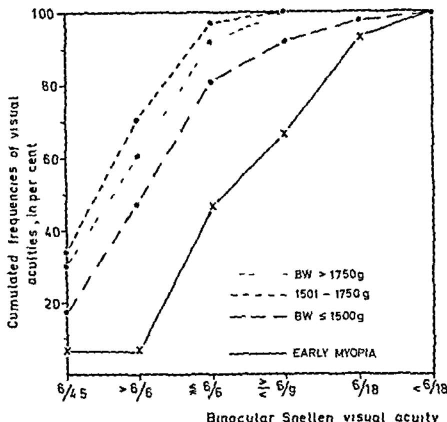


Figure 8 2 *Binocular corrected visual acuity* in the premature group subdivided by the birth weight limits 1500 and 1750 g shown with broken lines
In addition the results for the prematures (n = 15) with pre school myopia (solid line)
Cumulated frequencies in per cent

weighing *over* 1500 g also differs significantly from the more optimal findings in the mature group

Fig 8 2 also presents a cumulated visual acuity frequency curve for the small fraction of prematures considered on the basis of refraction criteria (Chapter 5) to have suffered ocular damage from their prematurity the pre school myopes This group numbers only 15 individuals Therefore significance analyses were not carried out but the curve deviates markedly from that of the total premature group and is even somewhat below the frequency curve of the worst situated birth weight group (≤ 1500 g) whence the majority of the pre school myopes were recruited With regard to other myopes of the material (curves not traced) the corrected visual acuity findings corresponded accurately to the norms for the mature and premature groups

The results are given in Table 8 2 and in Figs 8.3 and 8 4 presented in the same way as the binocular findings – and affording entirely analogous conclusions

The number of eyes having a true visual defect is fairly small in both groups 3 8% of all premature eyes (n = 604) and 1 5% of the mature ones (n = 474) had a visual acuity below 6/18 In half these defective cases the visual acuity was ⩽3/60 while the remainder were in the weak sighted range

Table 8.2 *Corrected monocular Snellen visual acuity* for distance in the premature and mature group (left) and in the premature group subdivided by the birth weight limit 1500 g (right)
Frequencies in per cent

	Prematures n = 604 eyes	Matures n = 474 eyes	Prematures of birth weights ⩽1500 g n = 180 eyes	Prematures of birth weights >1500 g n = 424 eyes
6/4.5	14 9%	31 9%	9 4%	17 2%
>6/6	28 1%	40 7%	22 8%	30 3%
≦6/6	36 4%	19 4%	36 1%	36 7%
⋛6/9	12 7%	5 9%	16 7%	11 1%
6/12-6/18	4 0%	0 6%	5 0%	3 5%
6/24-6/60	1 7%	0 8%	3 9%	0 7%
3/60 to light perception	1 7%	0 6%	4 4%	0 5%
No light perception	0 5%		1 7%	

Visual acuity above 6/6 was more common ($p < 0\ 01$ χ^2 test) among the mature (72 6% of all eyes) than among the premature group (43%) Within the latter the birth weight group ⩽ 1500 g made the poorest score only 32% exhibiting a visual acuity better than 6/6

The cumulated frequency curve of the mature group (Fig 8.3) as compared with that of the premature group is of a significantly higher level ($p < 0\ 01$ Kolmogorov-Smirnov) Within the premature group (Fig 8 4) the children of the ⩽ 1500 g group were in a significantly poorer situation than those of the other two birth weight groups (1501 – 1750 g and > 1750 g) But again the poorer visual

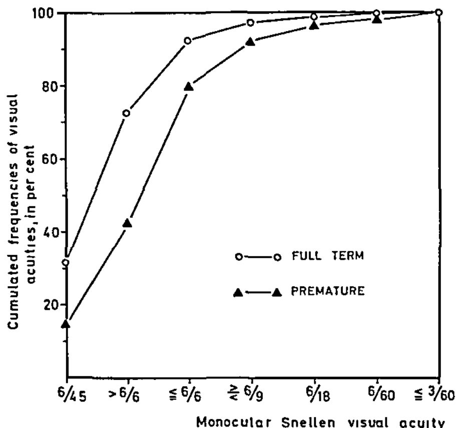


Figure 8.3 *Corrected visual acuity of single eyes* in children of the premature and mature group
Cumulated frequencies in per cent

result of the premature group could not be ascribed solely to the group ⩽ 1500 g Prematures weighing > 1500 g also showed a
significantly lower than that of the mature group

Fig 8 4 gives at the bottom the cumulated frequency curve for the 15 premature children with pre school myopia As in the binocular the curve was shifted towards lower values in relation to the total as well as the three premature birth weight sub-groups The results for *premature myopes (the eyes with school* myopia curve not traced) score i e even better than the most optimally placed premature birth group

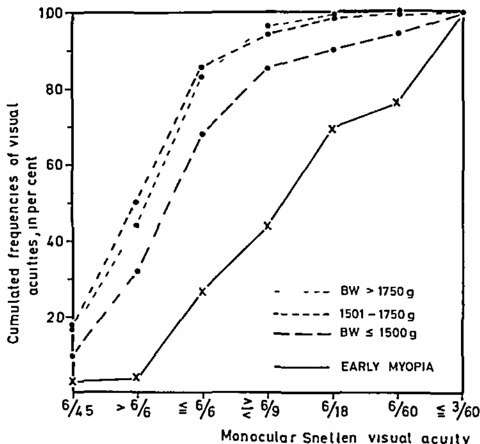


Figure 8 4 *Corrected visual acuity of single eyes* in the premature group subdivided according to the birth weight limits 1500 and 1750 g shown with broken lines

In addition the results for 30 eyes of 15 prematures with pre school myopia (solid line) *Cumulated frequencies* in per cent

Discussion

Binocular visual acuity is socially the most important parameter Considering several previous series of prematures with a high frequency of retrolental fibroplasia there is reason to note primarily the positive finding that in the present representative material of prematures 99% had good vision (≥ 6/18) Thus – judging by the ordinary visual criteria – nearly all the children are able to attend normal school without special measures for impaired sight

On the other hand the *1%* frequency of visual disablement in the premature group (viz a visual acuity ≤ 3/60) is high when compared with the incidence of

blindness among children in general An accurate total estimate cannot be given but on the basis of Danish and Swedish publications (Knudtzon 1942 Lindstedt 1969 Skydsgaard 1974) similar degrees of visual impairment may be expected in about 0.3 in 1000 This population estimate of course includes also premature children. Therefore the increased risk of blindness among the latter must be considered greater than that expressed merely by the ratio between the above-mentioned frequencies (1% and 0 03%) However the low prevalences do not justify such a purely numerical statement Suffice it to establish that the risk of severe visual defect in prematures of a low birth weight proved to be considerably higher than the risk estimated in the general population of the same age

At the other end of the scale the prematures more rarely achieved the two best scores 6/4 5 and > 6/6 However a visual acuity of ≤ 6/6 or better was obtained by 90% of the premature as compared with 97% of the mature group The latter percentage is in keeping with Holst & Tjåland (1962) who found that only 3% of a Norwegian school material could not attain a visual acuity of 6/6

When trying to figure out the visual cost of prematurity it seemed reasonable to include also *assessment of visual acuity in each eye separately* The argument is that retrolental fibroplasia may leave lesions of different severity on the two sides (Zacharias et al 1962) and something similar may apply to premature cataract and other anomalies arising or recorded perinatally In such cases the *total* ocular damage is not apparent from the binocular visual acuity which tells us nothing about the status of the poorer eye In view of the clearly increased incidence of heterotropia it is justified also to interpret – at least partially – the preponderance of squint amblyopia in prematures as a consequence of the prematurity Lastly it may be emphasized that a unilateral visual handicap places an individual in a poorer social position in the event of subsequent ocular trauma to or other pathology in the good eye

However the visual cost of prematurity proved to be relatively low also when assessed on the basis of the visual acuities in single eyes A true visual handicap was present in only a few per cent of all the eyes On the other hand the prematures had relatively fewer eyes with the most optimal vision scores 20% of the premature eyes could not attain 6/6 as compared with 8% of the mature eyes

Monocular visual acuities may be related to the results in a premature series previously reported by Zacharias et al (1962) Their series comprised a total of 446 eyes from children weighing at birth 4 lbs (1815 g) and less All were followed ophthalmoscopically during the first months of life The majority had no fundal changes or only very mild signs of retrolental fibroplasia Their subsequently measured corrected visual acuities were of a distribution consistent with the cumulated frequency curve in the present material for the fraction of prematures of a birth weight exceeding 1500 g According to Zacharias et al however 91 eyes showed evidence of moderate or severe active retrolental fibroplasia The cumulated frequency curve derived from their tables was – when compared with those of the present groups (cf Fig 8 4) – intermediate between my two poorest curves (i e worse than my birth weight group ≤ 1500 g but in a situation better than the small sub-group of pre school myopes)

On the whole it is apparent partly that a *true visual handicap* was present in only a very few of the children (with numerically small differences between the pre mature and the mature group) partly that an assessment of the *total* vision scale afforded definite evidence of a generally somewhat poorer visual performance in the prematures Within the most optimal part of the visual acuity range the pre mature group showed a significant shift towards lower values a shift with a clear relation to birth weight Thus the poorest total visual performance was observed among the prematures in the birth weight group ≤ 1500 g while the remaining part of the premature group was intermediate between this sub group and the mature group

Within the premature sample the small sub-group of 15 children with pre-school myopia gave a particularly poor visual performance This is at variance with the other myopes of the material who exhibited with optimal correction a visual acuity up to that among the remaining children Incidentally, it was not possible to demonstrate a negative influence upon visual acuity in other sub-groups with risk factors viz (a) maternal proteinuria anaemia smoking social class, (b) neonatal asphyxia oxygen therapy jaundice early symptoms from the central nervous system)

Except for the small group of pre-school myopes *refraction anomalies* did not influence the conclusions based upon the comparison of the premature with the mature group In part it was attempted to eliminate the influence of ametropia by glass correction and in part the two main groups did not show major inequalities in refraction pattern (Chapter 5) The only real difference between the groups was due to the sub-group of prematures with early myopia However they were so few (15 out of 302) that their deviating visual performance should not markedly affect the result in the *total* premature group

Let it be pointed out finally with reference to the review of the literature in the introduction that *age-conditioned* differences in visual performance could not be expected within the material The dispersion around the mean age of roughly 10 years was slight and even the youngest children included in the material were supposed to have attained their adult visual acuity

On the background outlined above it seems reasonable to point out *prematurity per se* as the actual cause of the generally somewhat poorer visual performance in the group Except in the few cases of retrolental fibroplasia (Chapter 10) however it has not been possible to deduce the specific nature – or anatomical site – of the relative defect in the prematures In this connection it must be borne in mind that the conventional visual fraction primarily reflects foveal resolving power in a standard test situation but that cerebral function – in the widest sense of the concept – is a decisive factor too Accordingly it can merely be established that the trauma of prematurity has entailed a lesser degree of perfection of that oculo-cerebral function which manifests itself in the Snellen visual acuity

Summary and Conclusions

Three premature children – one per cent of the total – had to be classified as *blind* having an optimally corrected visual acuity of 3/60 or less Two of them had retrolental fibroplasia and one congenital cataract Considering the estimated prevalence of blindness of around 0.3 in 1000 among children of the general population the risk of blindness in prematures of low birth weight is regarded as essentially increased

No children of the material were within the so-called weaksighted range (6/24 – 6/60) This means that 99% of the premature children (n = 302) and all mature control children (n = 237) had what may be considered socially good vision (≥ 6/18)

There was a somewhat higher percentage of *eyes* (than of individuals) with visual defect 3 8% of all premature eyes (n = 604) and 1 5% of all mature eyes (n = 474) had visual acuity below 6/18 These eyes were distributed in both groups equally on values in the weaksighted range and values ≤ 3/60

Thus the differences between the premature and the mature group were slight and not significant when assessed on the basis of the low frequency of true visual defect On the other hand there was a significant difference between the groups when the whole range of visual acuity was analysed In the case of binocular as well as monocular corrected visual acuity the prematures had less often high scores (6/4 5 and > 6/6) i e a significant shift towards somewhat poorer – but still socially satisfactory – visual performances

Among the prematures the sub-group of a birth weight ≤ 1500 g gave a poorer total visual performance than the remaining part of the prematures Out of the entire material with all its analysed sub-groups at risk only the small fraction of prematures with early myopia (n = 15) had a total visual performance below the norm set by the main group in question

Prematurity as such is held responsible for the generally somewhat poorer visual performance of the premature group

CHAPTER 9

BINOCULARITY

Introduction

If an association between prematurity and heterotropia is to be outlined on the basis of the literature such a presentation would be complex – for several reasons

Different Composition of the Materials

(a) Some publications are based upon *population studies* others upon *series from eye clinics*.

(b) The studies are of *children from different epochs* of neonatology – with consequent differences in mortality and morbidity This has influenced the composition of premature series as well as the degree and nature of any handicaps

(c) *Definition by birth weight has varied*

(d) *Age grouping is widely varied* (0 – 18 years) This is unfortunate as heterotropia is not always congenital and constantly present but manifests itself at different junctures and often changes as time goes by Some types subside with the maturation of binocular function which takes place up to the age of 7 – 9 years other types are not recognized until later This weakens materials with a wide age range and renders problematic the comparison of series differing in age

(e) *Geographic differences* The prevalence of heterotropia seems to be subject to some geographic variation

Differences in Methods of Examination and Diagnostic Criteria

Various publications are of course characterized by the authors presuppositions and primary aim Some studies have a definitely paediatric others an ophthalmological or directly orthoptic aim

The above items again emphasize the importance of control groups of the same age examined by a parallel technique and on the whole under analogous conditions

Prevalence of Heterotropia in the General Population

For Denmark this has been best elucidated by Frandsen (1958 1960) who found squint in 4 5% of approx 14 000 children in nursery schools and normal school The prevalence increased from 1% in the first year of life to a maximum of 7% among the 6 7 year-olds whereupon it tended to decrease The study programme comprised Hirschberg s test and cover tests but no sensory binocular tests

In Danish 7 16 year-olds school medical officers have found 5 2% (Knudtzon 1941) and 4 1% (Øster & Kjærgaard 1964) Engbæk (1970) reported a prevalence of 3 7% among children in the first form which in Denmark means an age of 7

Nordlow (1964) found 4% squinters among Swedish school children Lower prevalences have been reported by school medical officers in Norway and Finland viz 1 – 2% (Holst & Tjåland 1962) and around 1% (Heinonen 1947)

Smith (1969) reported a prevalence of squint of 4 5% among British school children in Birmingham whereas McNeil s (1955) 2 7% was closer to Thomson s (1924) and Douglas (1960) British population estimate of 2 3%

Jaeger (1963) in Germany and Franceschetti et al (1966) in Switzerland estimated a prevalence of about 3 5% among children Blazsó & Giesel (1971) found 7% squinters among Hungarian children (aged 6 15) and Litvinova (1964) 2 5% among 3 7 year-old Russian children From Israel a prevalence of 2 1% has been reported for children under 2½ years of age (Neumann et al 1971) and of 3% for 3-6 year olds (Nawratzki & Oliver 1970) In Arctic Canada Wyatt & Boyd (1973) found 1 5% squinters in the age range up to 10 years

Summing up the prevalence of heterotropia among school children in a number of countries seems to be around 3 5% It is not possible to ascertain whether the geographic differences are real or due solely to differences in testing conditions and criteria of selection

Frequency of Heterotropia Among Prematures

Table 9 1 lists the results from a number of studies the majority of which have been primarily paediatric (Nos 1 2 3 5 8 9 in the table) without systematic ophthalmological examination Moreover diagnostic criteria and the nature of the examinations for heterotropia have not been stated

The five ophthalmological studies (Nos 4 6 7 10 and 11 in the table) differ mutually in a number of the items mentioned above Controls have seldom been available and the authors have only been able to compare their frequencies of heterotropia in prematures with the not too definitely fixed prevalence in the population

The tendency increased frequency of heterotropia with decreasing birth weight *is apparent especially from the studies in which the prematures have been classified* into sub groups by birth weight the lowest birth weight groups having the highest

Table 9 1 *Prevalence of squint in earlier premature series*

	Premature series		Control series	
	n = number examined Age at examination Birth weight limit when different from the usual 2500 g	Prevalence of squint in per cent	n = number examined Age at examination	Prevalence of squint in per cent
1) Hess Mohr & Bartelme 1934	n = 250 age ≦ 8 years	14 4%	= 156 siblings of the premature propositi	1 3%
2) Schoberlein 1938	n = 96 school age	22 9%		
3) Brander 1940	n = 375 6 15 years	5 3%		
4) Eames 1946	n = 155 5 17 years	3 0%	n = 439 full term infants 5 17 years	2 4%
5) Hess & Lundeen 1949	n = 216 mainly 0 19 years BW less than 1250 g	18 1%		
6) Castren 1955	n = 480 1 18 years	4 6%	n = 237 full term infants 7 15 years	2 3%
7) Zacharias et al 1962	n = 229 about five years old BW > 1815 g (4 lb)	12 7%		
8) Drillien 1964	n = 514 0 8 years	8 8%		
9) McDonald 1967	n about 1 080 7-8 years BW < 1815 g (4 lb)	about 10%		
10) Douglas 1969	n = 104 about 8 years	10%		
11) Möller 1970	n = 640 3 5 years	12 5%		

frequency of squint (Nos 3, 6 and 8 in the table) The prematures in Zacharias et al s (1962) material may be classified according to whether or not there had been ophthalmoscopic signs of active retrolental fibroplasia during the neonatal period In their material the frequency of heterotropia was significantly higher in the fraction *with* than in that without such signs

Table 9 1 does not afford a direct proof that heterotropia is more common in premature than in mature children but according to the figures listed this is extremely likely

Frequency of Prematurity in Materials with Heterotropia

The increased frequency of heterotropia among children of low birth weight is reflected also in the reverse finding A higher frequency of prematurity in materials of children with than without heterotropia Such analyses are less sensitive to differences in squint criteria age distribution etc between materials The difficulty consists in procuring in retrospect reliable information about birth weight and other perinatal factors (as is apparent from the papers of Heinonen (1947) and Scobee 1951)

In three Scandinavian squint series (Heinonen 1947, Frandsen 1960 Nordlow 1964) 8 8 11 8 and 7 4% respectively of the children were premature The prematurity rates in the populations of the areas concerned were estimated to be somewhat lower viz 5% 5-6% and 2 8% In a Hungarian school series of approx 4 000 children Blazcó & Giesel (1971) reported a birth weight lower than 2 600 g in 18 4% of the children with heterotropia as compared with 10% in those without Neumann et al (1971) ascertained prematurity in 12 3% of 82 children in whom heterotropia had been diagnosed at population screening

Let me add three series from eye clinics In 230 out of 588 patients with heterotropia Scobee (1951) could establish the birth weight with sufficient certainty 13 5% had been born prematurely Among 100 patients with exotropia Dunlap & Gaffney (1963) found 12 prematures Fletcher & Silverman (1966) reported 13% prematures among 472 consecutive patients with esodeviations

Heterotropia Damage to the Central Nervous System and Prematurity

Most cases of heterotropia arise through an interaction of several factors (inherited and exogenous) entailing deficient development of binocular vision (Hugonnier & Hugonnier 1969) Binocular function may be regarded as a conditioned reflex disturbances may affect the afferent as well as the efferent paths and there may also be *central lesions Among the latter Heinonen (1947)* in particular has emphasized the importance of perinatal cerebral haemorrhage

In the above mentioned group of school children Blazcó & Giesel (1971) found that the squinting fraction had a massive preponderance above non squinters of psychic or sensory disturbances and even more often symptoms indicating pre

viously damaged motor function" Thus *heterotropia without such attendant signs* might be interpreted as a solitary late sequel to early cerebral damage A practical expression of such a view is that in several publications heterotropia has been included in score systems of cerebral damage (cf int al Heimer et al 1964 Schiottz-Christen sen 1973)

Instead of being only an isolated sign of possible brain damage squint may also be a more subordinate link in entities of indubitably cerebral nature (cerebral palsy and similar severe defects) The role of prematurity in such entities which are often combined with a squint will be briefly reviewed

In a large Danish material of cerebral palsy (Hansen 1960) almost 25% had been of a birth weight lower than 2500 g Prematurity was most common in the subgroups of spastic di and tetraplegia and in these very children the frequency of heterotropia (50%) was far above that in the total series (21%) Thus heterotropia was of an increased frequency in those types of cerebral palsy which were most often related to premature birth Smith (1963) summed up the prevalence of squint in a number of studies on cerebral palsy in which it ranged from 17-60% This wide variation is attributed to int al the varying severity of cerebral palsy from series to series

As already hinted the various types of cerebral palsy are not equally related to prematurity and/or heterotropia the group of spastic di and tetraplegia seems to be particularly prone Ingram & Kerr (1954) were able to demonstrate a relationship between retrolental fibroplasia and cerebral diplegia – with prematurity and anoxia as the presumed common cause Plum (1956) reported a particularly high prevalence of a low birth weight in paraplegic children in 30% it had even been below 2000 g Fantl & Perlstein (1961) roughly divided patients with cerebral palsy into true spastics (often related to prematurity) and cases of dyskinesia (often a sequel to neonatal anoxia) The spastics showed a significantly higher prevalence of heterotropia (41%) than did the group of dyskinesia (17%) In McDonald s (1967) series of children of birth weight ≤ 1815 g (4 lbs) spastic diplegia predominated among the 6 5% who exhibited cerebral palsy According to Glenting (1970) it was likely that prematurity *per se* might predispose to central nervous system damage although exact mechanisms could not be pointed out

Chapter 1 enumerated a number of studies demonstrating cerebral sequelae to low birth weight other than cerebral palsy viz intelligence defects mental disturbances etc Indeed in such children a number of workers have found heterotropia int al Frandsen (1960) She demonstrated the highest prevalence of heterotropia in the mentally poorest group

The results of Ingram & Kerr (1954) raise the question whether the violent retinal reactions in retrolental fibroplasia may have vascular counterparts in the brain itself – causing e g cerebral palsy and heterotropia However the literature has not supplied direct evidence of such vascular lesions outside the eye Zacharias et al s (1962) *results might* be taken indirectly to support the hypothesis heterotropia was particularly common among the prematures who had exhibited neonatal signs of active retrolental fibroplasia but this does not necessarily imply central damage A

number of these cases of heterotropia may be naturally explained by the ocular lesions affecting the afferent reflex arc of binocular vision

Distribution of Eso and Exodeviation

Among a series of cerebral palsy Douglas (1960) found heterotropia in 46% Among the 52 patients with concomitant heterotropia the ratio between a convergent and divergent squint was 2 7 1 This is far from the – very high – ratio of 10 1 which Douglas felt applied to squinters in the general population

Douglas findings suggest that various forms of brain damage – some of which are obviously related to prematurity – do not merely promote the development of heterotropia but thereamongst especially exodeviations Some support may be had in Jaeger s (1963) figures also applying to squinting children with cerebral palsy In his series the ratio eso exo was 2 2 1 but the calculations were based on only 16 cases In Harley s (1969) series of cerebral palsy the ratio was somewhat higher (5 8 1) A large group of children with less specific manifestations of cerebral disease was studied by Frandsen (1960) Among mentally retarded and mentally defective children with squint (n = 205) she found approximately the same ratio between eso and exodeviation as among so-called normal squinters

Douglas (1960) did not mention his source of the above mentioned ratio 10 1 of eso and exotropia among normal squinters Offhand this estimate seems rather high A further evaluation of this question however presupposes a knowledge of the *frequency of the various types of heterotropia in the population* This requires very large random samples to secure sizable sub-groups

Instead it is attempted to obtain a population estimate by analysing the figures from a number of reported series of heterotropia listed in Table 9 2 Appreciable differences between the results can be explained at least partially by different ages (a relatively larger number of exodeviations with increasing age) and different criteria of heterotropia Especially the latter factor must have been operative For instance the majority of exotropias are intermittent according to Schlossman & Borochoff (1955) 85% A ratio of e g 3 1 between eso and exotropia with manifest as well as intermittent cases included will be altered to 20 1 if intermittent exotropias are overlooked or omitted Nawratzki & Oliver (1970) even felt that a still higher proportion of exotropias were intermittent in their own material 96% Indeed, their classification resulted in a ratio as low as 1 2 1 However by far the great majority of publications do not afford data to clarify these matters

On the basis of Table 9 2 it may be estimated that about 15 30% of all horizon tal heterotropias are exotropias but it is evident also that a more exact population norm for the ratio between eso and exodeviations cannot be stated

In *premature materials* too the ratio between the two horizontal types of het erotropia differs and apparently within the range of the loosely outlined population norms Some groups of premature squinters are assembled in Table 9 3 which is *characterized above all by series so small that it is not possible to draw general con* clusions concerning the ratio between eso and exotropia in prematures This also

Table 9 2 *Ratio between eso- and exotropia* (relative prevalence of convergent and divergent strabismus) in some materials from the literature

Authors	Source of squint material	Number of squint cases in the materials	Ratio eso exo (tropia)
Cass (1937)	eye clinic	n = 461	4 3 1
Downing (1945)	American selectees	n = 1245	2 2 1
Scobee (1951)	(a) eye clinic material (b) premature infants among (a)	n = 588 n = 31	4 6 1 9 3 1
Schlossman & Borochoff (1955)	eye clinic	n = 1431	3 4 1
Crone & Velzeboer (1956)	population	n = 914	16 0 1
Frandsen (1960)	(a) *normal population* (b) mental defectives	*n* = 641 n = 205	3 7 1 3 0 1
Nordlöw (1964)	population	n = 229	7 8 1
Nawratzki & Oliver (1970)	population (pre school age)	n = 107	1 2 1
Neumann et al (1971)	population 1 2¹/₂ years old	n = 133	2 4 1
Blazso & Giesel (1971)	population (school age)	n = 287	3 9 1
Wyatt & Boyd (1973)	population (a) 0-9 years old (b) 10 19 years old	 n = 24 n = 31	 1 4 1 0 3 1

applies to the two series with parallel control groups of full term children (Eames 1946 Castrén 1955)

The distribution on the various types of *heterophoria* is even more difficult to clarify In most cases heterophoria must be regarded as a physiological state and again its diagnosis depends entirely upon the methods used A systematic investigation of heterophoria in a group of healthy children without manifest squint has

Table 9 3 *Ratio between eso and exotropia in some premature series from the literature*
BW = birth weights n = number of cases with heterotropia

	Premature squint series with birth weight limits	Ratio esotropia exotropia	Control "normal" squint series (full term)	Ratio esotropia exotropia
Eames (1946)	n = 5 BW<2500 g	1 5 1	n = 11	1 8 1
Hess & Lundeen (1949)	n = 39 BW<1250 g	3 3 1		
Scobee (1951)	n = 31 BW<2500 g	9 3 1	n = 588	4 6 1
Castrén (1955)	n = 22 BW<2500 g	1 0 1	n = 5	1 5 1
Möller (1970)	n = 76 BW<2500 g	3 0 1		

been reported by Doden & Protonotarios (1960) Using the Maddox wing (hetero phoria for near) they found a ratio eso exophoria of 1 3 8 and using the Maddox rod (heterophoria for distance) the ratio 1 9 1 Heterophoria in prematures and in full term control children was studied by Castrén (1955) but the data concerning technique of examination were not specified (synoptophore examination) so that it is difficult to assess the findings In Castrén s material there was a tendency to a more common occurrence of exophoria with increasing birth weight but the dif ference between the distribution of the various types of heterophoria in premature and mature children was not significant

Summary of the Literature

The items in the review of the literature may be briefly summed up

Comparing different squint materials is difficult because of pronounced dif ferences in recruiting the materials and in diagnosing heterotropia Besides the demand for comparable control groups has seldom been fulfilled

The prevalence of heterotropia among school children is presumably in the range 3 5% It is increased in materials of prematures and (the other way about) materials of squinters show a higher incidence of premature birth than does the general popu

lation Among premature children with active retrolental fibroplasia the frequency of heterotropia increases with the severity of the permanent retinal changes

Among the numerous causes of heterotropia brain damage may be considered This has been substantiated by materials of children with cerebral palsy and other cerebral damage Heterotropia is particularly common in the sub-groups of cerebral palsy in which premature birth is most common

One study revealed a relatively more common occurrence of *divergent* squint among squinters with cerebral palsy On the basis of the polymorphous literature it is not possible to supply a consistent answer to the question Whether the mutual distribution of the horizontal types of heterotropia are affected by early brain lesions and/or prematurity

Definitions and Methods Used in the Present Studies

Heterotropia = manifest squint A state in which the optic axis of only one eye is directed at the point of fixation Heterotropias may be *constant* or *intermittent* In analysing the material the intermittent deviations were included as heterotropia and the same applies to the cases with small squint angles (5° and less) The term *micro tropia* is deliberately not used as this concept also presupposes that retinal correspondence has been definitely recorded — Squint angles of less than 1 2° will hardly be recognized by the diagnostic methods used

Heterophoria = latent squint A state in which the eyes deviate only when dissociated in some test situation where fusion is rendered impossible Under normal binocular conditions fusion keeps the two optic axes directed simultaneously at the point of fixation

Orthophoria a theoretical ideal state The optic axes do not deviate in the test even though the fusion mechanism is broken by dissociation of the eyes

The prefixes *eso* and *exo* signify outward and inward deviation respectively whereas vertical imbalance is expressed by the prefixes *hyper* and *hypo*

The above deviations are usually measured in *prism dioptres (pd)* 2 pd correspond to one degree

Heterophorias are usually interpretable as physiological They cause symptoms only if the fusion mechanism is unable to compensate willingly for the basic motor imbalance Small phorias in particular are normal findings and orthophoria is merely considered a step midway on the normal scale Ordinarily there is no sense in setting up sharp limits — e g measured in pd — between normal and too large phorias because the fusion reserves vary individually In the present analysis however it was considered expedient to group the findings according to an arbitrary limit between physiological and unphysiological heterophoria As the material is a Danish one I selected the same fairly narrow limits as did Norn Rindziunski & Skydsgaard (1969) in an ophthalmological-orthoptic assessment of dyslectic children these authors classified the results as *physiological* if the Maddox wing showed *exophoria of* $\leqslant$ *6 pd esophoria* $\leqslant$ *4 pd and hyperphoria* $\leqslant$ *1 pd*. I adopted these limits — but included also the results of the other tests for phoria If only one of

these tests showed *exophoria > 6 pd esophoria > 4 pd or hyperphoria > 1 pd the values were classified as unphysiological*

The following tests were used in examining for motor imbalance (tropia/phoria)

(1) *Cover tests* fixating a light at 6 m and at 30 cm distance *Alternating cover* for phoria and monolateral *cover/uncover* alternately of each eye for tropia With a prism rod the motor imbalance was measured in pd Accommodative object for near was not used

(2) *Maddox cross at 5 metres with Maddox rod in a test frame Results in pd* Only horizontal imbalance was measured

(3) *Maddox wing* for the near situation results in pd Horizontal as well as vertical imbalance was assessed

To the motor binocular tests was added

(4) Determination of the *near point of convergence* (NPC) with R A F ruler and stated in cm This equipment was also used for determining the *near point of accommodation* (NPA) for each eye separately, using the letter chart of the apparatus as a fixation object The smallest or next smallest row of letters was used for the NPA determination

Sensory binocular function was elucidated by the following tests

(1) *Worth s four dots at 6 m and 30 m distance* (with red-green glasses as dissociation)

(2) *Wirt s stereotest (Titmus charts and glasses)* under conditions corresponding to the ordinary reading situation The eyes are dissociated by the spectacles with polarized glasses and the stereoscopic effect is obtained by the slightly disparate retinal images At the prescribed distance to the chart a stereoscopic interpretation of the finest symbols is stated to correspond to a stereoptic angle of 40 50 This is normally expected only with two intact and corresponding maculae

(3) *Synoptophore examination* (Clement Clarke Synoptophore) It is expected that during this test the eyes are adjusted to ∞ but it is difficult to exclude entirely accommodation and thereby nearness The main emphasis in this test was on the subjective statement of binocularity – in particular the possibilities of bifoveal vision

Grade I binocular vision simultaneous perception Slides Lion/cage Small objects are used to reflect macular co function The thing is to see the lion correctly in the cage Thus simultaneous perception here is taken in a somewhat stricter (more perfect) sense than the etymological implications of the word

Grade II binocular vision fusion Slides ' Cat without tail/cat without ear in small size First it was established whether the child could achieve fusion at all Thereafter the fusion amplitude was assessed

Grade III binocular vision stereopsis Slides The so-called Chavasse rings (from Hamblin cf pp 407-408 in Duke Elder s System of Ophthalmology Vol VI 1973) According to Snellen s principle the stereoscopic visual acuity is stated in values from 1/60 to 6/6 according to the visual angle from which the details of the rings have been seen – and interpreted as disparate This angle is 1' for the smallest set of rings corresponding approximately to the last two sets of rings on the Titmus chart

A further determination of the retinal *correspondence* of the two eyes was *not*

attempted – int al because the binocularity tests were carried out at a time of the examination programme at which some ocular fatigue may have been operative at least in some of the children However the type of correspondence will be apparent at least to some extent from the data presented For instance there were cases in which rough stereopsis was possible despite manifest heterotropia with amblyopia/suppression presumably by virtue of anomalous retinal correspondence These approaches were not followed by supplementary and repeated examinations of the children concerned

Further Comments on the Test Situations

It was endeavoured to carry out the tests under conditions as everyday as possible This means that

(1) The binocular tests were carried out without medication i e prior to the instillation of cycloplegics

(2) *The tests were performed with the eyes in mid position The examination* was not extended by systematic measurements in *other* gaze directions Thus e g A and V types of heterotropia were not assessed

(3) Glasses were usually offered only if the child was already wearing glasses This was preferred because it is not possible to emmetropize the children uniformly with glasses at a time when cycloplegic refraction is still unknown In other words the children were not systematically adjusted optically to zero This has no doubt influ enced the results of the various test For instance a child with physiological exophoria (≤ 6 pd) for near may easily have had an unphysiological value after correc tion of existing hypermetropia Moreover the determination of the NPA is affected At the analysis this was roughly classified as being greater or lesser than 8 cm the uncorrected myopic eye can more easily pass than the uncorrected hypermetropic eye If the NPA was farther than 8 cm however the examination was repeated with the subjectively accepted distance correction

As far as possible all the children had all the tests but as already mentioned the synoptophore and Worth s four dots at 6 m had to be omitted in the case of the 30 premature children who were examined in their homes Therefore the total number of children examined may fluctuate from table to table The same applies within the group of synoptophore-examined children because when the project was started it was stated merely whether or not fusion was present It was not until later that assessment of the horizontal fusion amplitude was entered into the stan dard procedure

Finally it may be emphasized that the classification of binocular functions into motor and sensory is fundamentally unnatural since we are dealing with intricate reflex mechanisms with afferent and efferent paths Lesions at various sites in the course of the reflex arc may afford fairly similar results in the clinical tests and in *general it is not possible to express the binocular function* of an individual by a single test This would really require a number of individually adapted test situations which should moreover be scattered over several sittings The reason as stated by Hugon

nier & Hugonnier (1969) is that the clinical binocular status – especially in children – may vary and need not necessarily reflect the function under the relevant practical circumstances

Such diagnostic individualization was not possible in the present project in which the tests had to be carried through in the course of the one consultation which was allotted for each child The main emphasis was on obtaining by uniform data a reasonable elucidation of the question by the aid of a fairly wide but fixed assort ment of tests

Present Results

'Motor' Tests

Table 9 4 sets out the frequency of the theoretical ideal condition *orthophoria* in the present material It also demonstrates the dependence of the selected diagnostic procedures including the distance to the object (near or distant) The Maddox wing and Maddox rod proved definitely more sensitive than the coarser cover tests Only a small number of the children had orthophoria in all tests viz 15 9% of the pre mature and 11 4% of the mature ones This difference is not statistically signifi cant, further the comparison is not quite justified *as at least some of the premature*

Table 9 4 *Prevalence* (in per cent) *of orthophoria at various tests*
n = number of children tested in the premature and mature group

		Prematures	Matures
For distance	Cover/uncover test	72 1% n = 302	86 5% n = 237
	Maddox rod	30 6% n = 268	37 9% n = 237
For near	Cover/uncover test	42 9% n = 302	44 7% n = 237
	Maddox wing	26 6% n = 271	25 3% n = 237
"Overall orthophoria" (i.e. when all motor tests showed orthophoria)		15 9% n = 302	11 4% n = 237

children with orthophoria were only thus classified because they did not have the more sensitive Maddox tests

The *heterophorias* were divided into physiological and so-called unphysiological (p 135) The values above physiological limits (phorias exceeding the limits of 4 pd eso- 6 pd exo- and 1 pd hyper in at least one of the four tests) occurred more often for near than for distant object Considering the total material unphysiological values were found in 60 children by the Maddox wing and in 43 by alternating cover test for near At distance 23 cases were found by the Maddox rod and 7 by alter nating cover The tests overlapped to a marked extent A total of 62 children had unphysiological phoria in one or more tests without a difference in the frequency between the premature (11 9%) and mature group (11%)

Table 9 5 *Binocular motor balance* as estimated by the tests described in the text in the premature and mature group (top) and in subdivisions of the premature group according to birth weight (bottom) Number in each diagnostic group frequencies in per cent

	Ortho phoria	Heterophoria physiological values	Heterophoria unphysio- logical values	Heterotropia
Premature group n = 302	48 (15 9%)	150 (49 7%)	36 (11 9%)	68 (22 5%)
Mature group n = 237	27 (11 4%)	170 (71 7%)	26 (11 0%)	14 (5 9%)
Prematures of BW ≤ 1500 g n = 90	12 (13 3%)	41 (45 6%)	15 (16 7%)	22 (24 4%)
Prematures of BW 1501 - 1750 g n = 93	17 (18 3%)	43 (46 2%)	10 (10 8%)	23 (24 7%)
Prematures of BW > 1750 g n = 119	19 (16 0%)	66 (55 5%)	11 (9 2%)	23 (19 3%)

The total distribution of the binocular motor diagnoses is given in Table 9 5 which includes also the *heterotropias* The distribution of the premature group on the four diagnostic categories differs significantly ($p < 0\,01$, χ^2 test) from that of the mature group due primarily to marked differences in the frequency of hetero

tropia and physiological phoria It will be seen that *heterotropia* was almost four *times more common among the prematures (22 5%) than among the matures (5 9%)*

Table 9 5 also demonstrates the results for the premature group by *birth weight* Between the three birth weight groups ($\leqslant 1500$ g 1501 – 1750 g and > 1750 g) there is no significant difference in the distribution of the motor diagnoses The group of highest birth weight (> 1750 g) gets closest to the mature group but still differs significantly from it at the 0 01 level

The frequencies were analysed also after dividing the two main groups by sex This showed no sex differences in the distribution of heterotropia and the three types of phoria

Vertical imbalance of the ocular muscles was observed in only a few cases 13 instances of hypertropia were distributed on 10 premature and 3 mature children Hypertropia did not occur isolated but combined with – a generally predominant – *horizontal heterotropia Hyperphoria of 2 pd and more was found in a total of 6* children 5 of whom were of the premature group

In other words horizontal deviations were all predominant The *ratio between eso and exo deviations* was studied for tropias as well as phorias for near as well as

Table 9 6 *Ratio between eso and exodeviations* in the premature and mature group of the material recorded according to the diagnostic tests employed
Heterotropia (left) and heterophoria (right)
n = number of cases with deviation in each group

		Heterotropia		Heterophoria	
		Prematures	Matures	Prematures	Matures
With distant object	Cover/uncover and alternating cover test	1 7 1 n = 67	1 3 1 n = 14	1 2 1 n = 16	1 8 1 n = 17
	Maddox rod			2 2 1 n = 129	2 5 1 n = 127
With near object	Cover/uncover and alternating cover test	1 6 1 n = 66	2 0 1 n = 12	1 6 5 n = 105	1 5 0 n = 119
	Maddox wing			1 4 8 *n = 145*	1 5 5 *n = 162*

Table 9 7 *Near point of convergence* (NPC top) and *near point of accomodation* (NPA bottom) in 301 premature and 237 mature children Number of children (for NPC) and number of eyes (for NPA) Frequencies in per cent

	Prematures		Matures	
NPC better than 8 cm	249	(83 0%)	222	(93 7%)
NPC 8 30 cm	19	(6 3%)	9	(3 8%)
NPC above 30 cm or "cannot"	32	(10 7%)	6	(2 5%)
NPA better than 8 cm	499	(83 0%)	428	(90 3%)
NPA above 8 cm	80	(13 3%)	40	(8 4%)
NPA could not be measured (deep amblyopia)	22	(3 7%)	6	(1 3%)

for distant (Table 9 6) In the case of the heterophorias there was a preponderance of esophoria for distant (eso exo 2 1) while at near this was reversed (eso exo 1 5 5) but without significant differences between the premature and mature group As for the heterotropias the fractions of the mature group were too small to justify further conclusions

Table 9 7 gives the results of determinations of the *near point of convergence and of accommodation* in the two main groups of which the premature group did worse ($p < 0\ 01$ χ^2 test)

In determining the NPC the convergence movement was observed but it was not possible to ascertain whether binocular fixation was actually present during the test For the premature group the figures show that 17% were *unable* to achieve a NPC better than 8 cm When also considering the 22 5% frequency of heterotropia it is apparent that several squinters must have yielded a satisfactory convergent movement In a few children with intermittent tropias there has been a question of regular bifoveal convergence In several cases of heterotropia however there was obvious suppression or amblyopia in such children anomalous correspondence may have been operative during the test while others have set up a deliberate squint as soon as they realized the object of the test

The NPA was determined for each eye separately As compared with the mature group the prematures exhibited a somewhat larger fraction of amblyopic eyes which did not achieve accommodation in the test (10 7% *versus* 2 5%) Omitting these amblyopic eyes prior to the significance calculation did not however alter the total result the premature group still being poorer under the conditions of the NPA test

Worth s Four Dots

The red-green spectacles afford effective dissociation of the visual impressions in the two eyes The correct answer – four dots – is given in cases with bifoveal binocular vision but may also occur in microtropia with harmonious anomalous correspon dence

Table 9 8 Results of the *Worth four dot test* performed for distance and near Frequencies in per cent

		Prematures n = 266 for distance 295 for near	Matures n = 234 for both distances
Distance	Four dots	70%	89%
	2 3 or 5 dots	30%	11%
Near	Four dots	76 6%	90%
	2 3 or 5 dots	23 4%	10%

About every four premature and every ten mature children reported seeing 2 3 or 5 dots in the test The difference between the two groups is significant at the 0 01 level (χ^2 test) Table 9 8 gives the exact frequency of a correct and wrong answer

Fusion (Assessed in Synoptophore)

270 of the premature children and all 237 mature children were tested for fusion in the synoptophore The findings are analysed quantitatively in Table 9 9 18 5% of the prematures tested and 5 5% of the matures could *not* achieve fusion in the test The difference between the groups is significant at the 0 01 level (χ^2 test)

When the premature group is divided by birth weight the table shows lacking fusion most often in the birth weight group $\leqslant$ 1500 g The tendency in the three birth weight groups could be confirmed by significance calculation ($p < 0\ 05$ χ^2 test) The $>$ 1750 g group was closest to the results of the mature children but without attaining their level

Table 9 9 Frequency of *lacking fusion* (per cent) *in the synoptophore*-examined fraction of the material Premature and mature group at top Subdivisions of the prematures by birth weight (bottom)

	Number examined in synoptphore	Percentage with no fusion
Prematures	270	18 5%
Matures	237	5 5%
Prematures of birth weight ≦1500g	81	27 2%
Prematures of birth weight 1501 1750 g	80	17 5%
Prematures of birth weight >1750 g	109	12 8%

Fusion was not assessed in the synoptophore in the 30 premature children examined in their homes but was indirectly elucidated by means of Wirt s stereopsis tests Five out of the 30 children achieved no stereopsis and another two only rough stereopsis At least the former five would hardly have achieved fusion in the synoptophore situation either When this estimate is included the frequency of lacking fusion in the entire premature group is 18.2% In other words there is no reason to believe that the fraction not studied by synoptophore would have altered the conclusions based upon Table 9.9

In the 81 children examined first (35 prematures and 46 matures) it was merely established whether fusion was present with the object size concerned For this part of the material the *fusional amplitude* was not measured but this was done in the remaining cases studied by synoptophore – as the distance in pd between the two extreme points within which fusion could be maintained The limits between the various fusional qualities were selected arbitrarily

(a) No fusion
(b) Poor fusion fusion amplitude less than 20 pd
(c) *Medium fusion fusion amplitude 20 – 35 pd*
(d) Good fusion fusion amplitude exceeding 35 pd

The results are shown in Table 9 10 As a group the prematures – with more poor and fewer good results – gave a significantly poorer performance (at the 0 01 level) than did the mature children This was due primarily to the much higher occurrence of no fusion" in the prematures but this was not the only cause of the skewness Thus if children *without* fusion are excluded from both groups in Table 9 10 and only the three categories of fusion are considered there is still a significant difference between the two groups but now only at the 0 05 level

Table 9 10 *Fusional capacity* estimated from the fusion amplitudes as measured by *synoptophore* Premature and mature groups (top) subdivisions of the prematures by birth weight (bottom)
Number of children frequencies in per cent

	No fusion	Poor fusion (<20 pd)	Medium fusion (20 35 pd)	Good fusion (>35 pd)
Prematures n = 235	50 (21 3%)	82 (34 9%)	51 (21 7%)	52 (22 1%)
Matures n = 191	13 (6 8%)	58 (30 4%)	62 (32 4%)	58 (30 4%)

Prematures of BW ≦1500 g n = 70	22 (31 4%)	16 (22 9%)	13 (18 6%)	19 (27 1%)
Prematures of BW 1501 1750 g n= 74	14 (18 9%)	32 (43 3%)	18 (24 3%)	10 (13 5%)
Prematures of BW >1750 g n = 91	14 (15 4%)	34 (37 4%)	20 (21 9%)	23 (25 3%)

Table 9 10 also sets out the corresponding findings within the premature group alone divided according to birth weight limits 1500 g and 1750 g The group of lowest birth weight gave the poorest fusion performance The three birth weight groups differed at the 0 05 level (χ test) Again the children without fusion load the significance calculation After omission of this fraction the difference between the three birth weight groups is no longer significant

Finally the fusion amplitudes were related to the binocular motor diagnoses The findings in the *heterotropic* children will be discussed later in this chapter The fraction of unphysiological *heterophorias* of the *total* material had significantly more often poor values (fusional amplitudes below 20 pd in 54% $n = 50$) than did the fraction with physiological heterophoria (33 4% $n = 293$) *The same conclusion* may be drawn for the premature group alone in which 60% of the unphysiological (n = 28) and 38% of the physiological heterophorias (n = 141) had fusion amplitudes below 20 pd When the mature group was assessed separately, there was not however a significant difference between the fusional findings in the same two motor sub groups

(A) *Wirt s Principle* (Titmus Charts) The findings were classified arbitrarily ac cording to the quality of stereopsis the child could achieve with Titmus charts

(a) No stereopsis
(b) Poor stereopsis – stereoptic perception of the big fly the animals or some of the first three rings
(c) Medium stereopsis – stating correctly rings 4 5 6 or 7
(d) Good stereopsis – stating correctly ring 8 and possibly also ring 9

The findings are presented in Table 9 11 The overall achievement in the pre mature group was significantly poorer than that of the mature group at the 0 01 level (χ^2 test) also when omitting the children who totally lacked stereopsis Thus stereopsis in the prematures was poorer both quantitatively and qualitatively than in the mature control group

Table 9 11 *Stereoptic visual capacity* as estimated by Wirt s principle *(Titmus plates)* in the premature and mature group (top) and in subdivisions of the premature group according to birth weight (bottom) Number of children in the diagnostic groups Frequencies in per cent

	No Titmus stereopsis	Poor stereop sis (Titmus fly animals or 1 3 rings	Medium stereopsis (also Titmus rings 4 7)	Good stereopsis (including rings 8 9)
Prematures n = 300	50 (16 7%)	30 (10%)	39 (13%)	181 (60 3%)
Matures n = 237	9 (3 8%)	11 (4 6%)	18 (7 6%)	199 (84%)
Prematures of BW ≤1500 g n = 89	20 (22 5%)	6 (6 7%)	11 (12 4%)	52 (58 4%)
Prematures of BW 1501 1750 g n = 93	14 (15 1%)	11 (11 8%)	13 (14%)	55 (59 2%)
Prematures of BW >1750 g n = 118	16 (13 6%)	13 (11%)	15 (12 7%)	74 (62 7%)

Table 9 11 also comprises the corresponding analysis solely for the children of the premature group, divided by birth weight limits 1500 g and 1750 g It is evident that the results in the three birth weight groups are very similar ($p > 0\ 05$ χ^2 test) Judging by the percentages the sub-group > 1750 g is closest to the mature group but the difference between this birth weight fraction and the mature group is still significant ($p < 0\ 01$, χ^2 test)

As in the case of fusion the association with the motor diagnoses was analysed The findings in the *heterotropic* children will be discussed later The distribution of the various stereoptic qualities proved to bear no significant relation to the degree of the *heterophoria* when classified as physiological or unphysiological

(B) *Synoptophore Assessment* (Chavasse Stereo Slides) This stereoptic assessment was more difficult for the children than the Titmus test The quality of stereopsis if present could be recorded as the Snellen fraction which was directly apparent from the stereoslides In practice it proved very difficult to obtain a stereoptic perception of the 6/6 figure even for children who managed the Titmus test with ease Accordingly the stereoptic findings were graded as follows (Table 9 12)

(a) No stereopsis
(b) Poor stereopsis – in the range 1/60 – 6/36
(c) Medium stereopsis – in the range 6/24 – 6/18
(d) Good stereopsis – 6/12 or better

As compared with the Titmus results rather more children lacked stereopsis and somewhat fewer had the best degrees of stereopsis Incidentally the results of the two stereoptic tests were in accurate agreement and this applies also to the birth weight and heterophoric sub-groups The conclusions from the synoptophore assessment with Chavasse stereo slides are the same as above for Titmus' charts

Binocular Vision Tests Considered Together

Table 9 13 aims at an overall assessment of the binocular vision tests whose results were listed individually in the seven preceding tables

The children not studied by synoptophore are classified according to the Titmus results Perfect stereopsis in the Titmus test is assigned to the group of most optimal binocular vision

Again the binocular performance in the premature group was significantly poorer than in the mature group ($p < 0\ 01$ χ^2 test) Within the premature group it was not possible to demonstrate a definite association between the quality of binocular function and birth weight ($p > 0\ 05$) The results in the three premature birth weight groups (≤ 1500 g 1501 – 1750 g and > 1750 g) did not differ significantly from each other

Some Items Further Elucidating the Children with Deviating Binocular Function

A number of clinical associations are of interest in assessing children with a squint A few such items will be outlined below

Table 9 12 *Stereoptic visual capacity* as estimated in *the synoptophore* with Chavasse stereo-slides (rings 1/60 to 6/6) in the premature and mature group (top) and in subdivisions of the premature group according to birth weight (bottom)
Number of children frequencies in per cent

	No stereopsis	Poor stereopsis (Chavasse rings 1/60 to 6/36)	Medium stereopsis (6/24 & 6/18)	Good stereopsis (6/12 and better)
Prematures examined in synoptophore n = 270	65 (24 1%)	30 (11 1%)	36 (13 3%)	139 (51 5%)
Matures examined in synoptophore n = 236	19 (8 1%)	11 (4 6%)	26 (11%)	180 (76 3%)
Prematures of BW ≦1500 g n = 81	24 *(29 6%)*	9 *(11 1%)*	11 *(13 6%)*	37 *(45 7%)*
Prematures of BW 1501 1750 g n = 80	19 (23 8%)	11 (13 8%)	13 (16 2%)	37 (46 3%)
Prematures of BW >1750 g n = 109	22 (20 2%)	10 (9 2%)	12 (11%)	65 (59 6%)

Concomitant incomitant squint
Constant intermittent squint and small squint angles
Correspondence findings assessable from the data
Squint amblyopia
Time at onset of squint
Hereditary predisposition
Refraction factors including anisometropia
Other possible aetiological factors.

Owing to the overlapping of the various tests of binocular function the group of children with abnormal binocularity was extended to comprise besides the cases of actual heterotropia also the few cases (5 in the premature and 3 in the mature group) in which the sensory tests showed severe defects but no significant motor disturbance These were children who could not achieve binocular vision in the tests employed or who had merely the coarsest form of binocular vision (e g in the case of Titmus fly) Thus defined the total group of 'binocular deviants numbers 73 premature and 17 mature children

Table 9 13 *Overall binocular vision* in the premature and mature group (top) and in subdivisions of the premature group by birth weight (bottom) *as estimated from the synoptophore and Titmus tests* Frequencies in per cent

	Binocular vision not obtained in the synoptophore or by the other tests performed	Binocular vision grade I II including some fusion but not stereopsis	Binocular vision grade I III but stereopsis imperfect	Optimal binocular vision including perfect (foveal) stereopsis
Prematures n = 301	18%	3%	30%	49%
Matures n = 237	5%	1%	16%	78%
Prematures of BW ≦1500 g n = 90	23%	3%	28%	46%
Prematures of BW 1501-1750 g n = 93	17%	3%	34%	4%
Prematures of BW >1750 g n = 118	14%	3%	28%	55%

Concomitant Incomitant Squint

In practically all cases the heterotropia was concomitant Only four children – all prematures – exhibited an incomitant element in all four the squint was subordinate

to other severe ocular abnormalities (Cases 1 3 5 31 Appendix) The material did not include cases of purely paralytic squint

Constant Intermittent Squint Small Squint Angles

Out of the 73 d viants of the *premature* group 20 children had squint angles of less than 5° It was difficult to decide on the basis of the motor tests whether the type of squint was to be classified as constant or intermittent In the remaining 53 the squint angle exceeded 5° distributed on 37 constant and 16 intermittent cases – Nine of the 73 children had previously undergone operation for their squint. According to the size of the *original* squint angle these 9 children were classified as constant squinters even though 7 of them exhibited minimal squint angles at the time of the present examination

In the *mature* group the 17 deviants were equally distributed on the same three categories (6 with squint angles of less than 5° and 11 exceeding 5° of the latter 6 were constant and 5 intermittent) None of the 17 mature children had previously been operated upon for their squint

Correspondence Findings Among the Squinters

In the majority of the binocular deviants the various tests showed conformable results but there were al o cases showing dissociation especially between the motor and "sensory" results For instance some children with heterotropia yielded different degrees of binocular vision a few even good stereopsis Reversely some children with lacking binocular vision showed orthophoria in the motor tests

The present data were not considered sufficient for classifying the individual cases according to detailed perceptual grading For illustrative purposes however a few values for the total material will be presented which int al contribute to explaining apparent discrepancies between the results of related tests

In the total group of *heterotropia* (n = 82) 30% were able to achieve fusion in the synoptophore assessment 37% showed stereopsis with Titmus charts and 14% with Chavasse stereo slides in the synoptophore However these were mainly cases of poor fusion or coarse stereopsis Medium or good stereopsis defined as in Tables 9 11 and 9 12 was achieved by 8 and 2 children respectively Because of the small number of children in these sub subgroups the influence of prematurity could not be further assessed

For comparison it may be mentioned that among the remainder of the material – i e the children with different degrees of *phoria* – good stereopsis was found in 96% with the Titmus charts and in 75% in the synoptophore The mature children – having more good and fewer poor binocular performances – did significantly better than the premature children

Amblyopia

Amblyopia signifies impaired vision, defined here with the better eye as reference At a side difference in optimally corrected visual acuity of more than two lines on Snellen s chart the poorer eye was designated amblyopic Using the named chart this means that an eye showing 6/12 might be recorded as amblyopic, but only in the event of 6/4 5 in the better eye

Amblyopia interpreted as secondary to heterotropia and/or high anisometropia was present in 35% of the premature and in 43% of the mature children in whom these states were present In five prematures on the other hand the squint had to be interpreted as being secondary to visual impairment of organic nature

Time at Onset of Squint

Information concerning this factor was often vague, and the figures in Table 9 14 do not pretend to be absolute According to this table, 59% of the premature cases of squint were considered congenital (detected within the first year of life) against 29% of the mature squinters However this marked difference between the two groups could not be confirmed statistically (χ^2 test) primarily because of the wide con findence range due to the small number of squinters in the mature group

Table 9 14 *Age when squint was first discovered*
Squint here designates heterotropia and/or severe binocular sensory defect Number of children

	Age at onset of squint		
	Within first year of life (or "always)	After the age of one year	Squint not dis covered before or information inconclusive
Prematures with squint n = 73	43	8	22
Matures with squint n = 17	5	8	4

Hereditary Predisposition

Hereditary predisposition to a squint was of the same extent in both *main* groups (prematures and matures) Between the premature and mature *squinters* there was also no difference in this respect judging by the data reported Within the premature group less than 40% (n = 73) reported a squint in the immediate family as compared with 47% of the mature squinters (n = 17) The uncertainty of the data concerning heredity should be borne in mind however

Refraction and Binocular Vision

Among squinting children esotropia usually predominates a type of squint often combined with refractive values on the hypermetropic side of the age norm This is indeed apparent from Tables 9 15 and 9 16 which give the refraction means and the distribution on the three main refraction groups When all eyes are divided into *refraction classes each of two dioptres (not tabulated)* the *heterotropic children* – within the premature as well as the mature group – show a significant shift towards hypermetropia as compared with the non heterotropic groups ($p < 0\ 01$ Kolmogorov-Smirnov) On the other hand there were no significant differences in the refraction spectrum related to the degree of *heterophoria*.

Table 9 15 *Mean ocular refraction* for eyes from the premature and mature group *subdivided according to the degree of motor imbalance*
Mean value in dioptres n = number of eyes

		Premature group	Mature group
Eyes of children with	Orthophoria and low (= physiological) heterophoria	+ 0 81 D n = 382	+ 0 91 D n = 388
	High heterophoria (= unphysiological)	+ 0 64 D n = 72	+ 1 29 D n = 52
	Heterotropia	+ 0 65 D n = 144	+ 2 45 D n = 34

Special assessment of the distribution of refraction values in heterotropic children showed in the mature squinters a significant shift towards hypermetropia ($p = 0\ 025$) as compared with the premature ones – It is reasonable to assume that the present group of premature squinters is composed of two fractions the usual refraction related ones and cases in which the role of refraction must be considered sub-

Table 9 16 *Distribution of eyes on three main refraction groups* in premature and mature group both *subdivided according to presence of heterotropia*

Incidences in per cent and number of eyes

		Myopia	Emmetropia and slight hypermetropia (0 to + 2 D)	Hypermetropia above + 2 D
Prematures	With heterotropia n = 144 eyes	14 6% 21	57 6% 83	27 8% 40
	Without heterotropia n = 454 eyes	13 0% 59	77 3% 351	9 7% 44
Matures	With heterotropia n = 34 eyes	5 9% 2	38 2% 13	55 9% 19
	Without heterotropia n = 440 eyes	9 5% 42	76 4% 336	14 1% 62

ordinate to some kind of special premature aetiology Such cases were recruited at least in part from the sub-group which judging by refractive criteria was considered to have suffered a prematurity" trauma viz the 15 pre school myopes (Chapter 5) 11 *of these 15 children had heterotropia and/or severe sensory binocular defect* and only 2 had perfect stereopsis The influence of special factors is also reflected by the relatively low mean refractive value for the total group of premature squinters (Table 9 15)

Anisometropia

Ten per cent of the binocular deviants had anisometropia with a side difference exceeding two dioptres In the remaining material only 1.3% had anisometropia of this magnitude Again the numbers are too small to permit further analysis after division by degree of maturity

Some Factors of Possible Aetiological Significance in Deviating Binocular Function

Among such factors two have already been discussed above viz (a) *hereditary predisposition* and (b) *refraction* Let us consider some further items which bear relation

to (c) *pregnancy* and to (d) the *clinical condition of the infant* at birth and during the first year of life

(c) *Pregnancy factors* The binocular findings were related to the following five factors

(1) Maternal smoking (2) maternal anaemia during pregnancy (3) maternal proteinuria during pregnancy (4) signs of maternal sensitization and (5) social status

For the first four items it was not possibl- to demonstrate any significant in fluence upon the child s subsequent binocular function

As concerns *social status* (cf also Chapters 2 and 14) the premature group and the mature group proved to be of nearly the same social composition. Both groups had a significant preponderance of children with binocular deviation in social classes IV – V as compared with classes I – III (where I is the highest and V the lowest social status) In classes IV – V the *squint* rate was 31% and 15% for prematures (n = 95) and matures (n = 80) respectively The corresponding prevalences for social classes I – III were 18% in prematures (n = 166) and less than 4% in matures (n = 138) – In other words there is a distinct association between heterotropia and social status but the social factors do not explain the *difference* in the squint rate between the premature and the mature group

(d) *Early clinical condition of the infants.* The binocular findings were related to the following three factors

(1) Early central nervous system damage (2) oxygen therapy and (3) neonatal jaundice

Table 9 17 *Some clinical conditions at birth or at the age of one year suggesting or indicating cerebral damage* (according to Zachau Christiansen 1972) in the premature and the mature group Frequencies in per cent, number of children with available data

	Prematures	Matures
Infant mildly or heavily affected clinically at birth	27 5% n = 265	8.2% n = 232
Asphyxia (more than one minute elapsing from birth of head until 10 respir)	25 4% n = 268	10.3% n = 234
Signs of neonatal brain damage	22 2% n = 297	11 0% n = 236
Motor retardation or presumed brain damage at the age of one year	25 0% n = 296	3 0% n = 235

The latter two items had no significant influence upon the children s subsequent binocular status In the case of oxygen therapy the groups were divided according to whether or not oxygen had been administered neonatally, in the case of jaundice according to whether or not the serum bilirubin had exceeded 20 mg/100 ml neonatally

Thus leaves the possible role of early *central nervous system damage* This item may be analysed on the basis of the clinical data concerning the infants condition

Table 9 18 *Binocular motor balance and sensory state in the premature group subdivided according to the presence of early neurological signs* Frequencies in per cent

	Premature infants			
	Neurologically evaluated in the first week of life		Neurologically evaluated at the age of one year	
	Signs of brain damage n = 65	No signs of brain damage n = 233	Signs of brain damage n = 74	No signs of brain damage n = 222
Orthophoria	15 4%	15 9%	12 2%	17 1%
Heterophoria physiological values	44 6%	51 1%	47 3%	50 5%
Heterophoria unphysiological values	18 5%	10 3%	12 2%	12 2%
Heterotropia	21 5%	22 7%	28 4%	20 3%
Binocular vision not obtained in the tests performed	18 2%	17 3%	20 3%	16 3%
Binocular vision grade I II	4 5%	3 0%	1 4%	1 4%
Binocular vision grade I III but stereopsis imperfect	31 8%	29 0%	37 8%	29 9%
Optimal binocular vision including perfect stereopsis	45 5%	50 7%	40 5%	52 5%

during the first year of life (Zachau-Christiansen 1972) Some such early findings are shown in Table 9 17 for the two groups of the present material The table lists (1) the infant s clinical condition at birth (2) asphyxia – assessed by the time elapsing from delivery of the head until 10 respirations had been drawn (3) neonatal signs of brain damage and (4) motor/cerebral negative deviation at follow up around the age of 1 year

According to these data about every fourth child of the premature group had to be considered "affected whereas this applied to only every tenth of the mature children The difference between the two main groups is significant ($p < 0\ 01$) for all four items

The four clinical parameters listed can be interpreted indirectly or directly as signs of possible early brain damage and of course there is appreciable mutual over lapping In the statistical assessment of the influence upon binocular functions I decided primarily to analyse on the basis of the more direct findings i e signs of *neonatal brain damage and signs of negative deviation at the 1 year follow up* Such an analysis is reasonable only in the premature group as the small number of deviating mature children does not permit division into diagnostic sub-groups

Table 9 18 presents the distribution of the various motor and sensory binocular findings in the present study among the neurologically affected and unaffected pre mature children Significance calculation did *not* afford evidence of the hypothesis that a disturbance of binocular function is more common in the neurologically af fected than in the neurologically unaffected fraction of the premature group (This aspect will be further discussed in Chapter 14)

Discussion

By the motor and sensory tests binocular defects were detected significantly more often in the prematures of the present material than in the control group of children born at term Heterotropia was observed in 22.5% of the prematures – or nearly four times as often as in the matures (5 9%) The squint rate among the latter was on the level estimated by Frandsen (1960) among *Danish* school children of about the same age viz around 10 years

The incidence of heterotropia in the prematures is high as compared with the results in the premature series listed in Table 9 1 several of which even had lower upper birth weight limits than the present material This difference may be real but no doubt the diagnostic method has influenced the number of detected cases of heterotropia For instance screening major series of children by non ophthalmo logical personnel (McDonald 1967 and others) *catches mostly cases of pronounced* squint Children with small squint angles and with intermittent heterotropia have no doubt often been recorded as binocularly normal and this results in too low a squint rate For example if only the manifest cases with squint angles exceeding 5° had been diagnosed in the present study the prevalences would have been 12 3% in prematures and 2 5% in matures These figures agree better with those in Table 9 1

Similar reflections apply to the heterophorias The results proved to be entirely

dependent upon the method used (Table 9 4) as previously demonstrated by several authors int al Weymouth (1916) Mellick (1949) and Tait (1951) Therefore undue importance should not be attached to the present division into physiological and unphysiological phoria based on single measurements and fixed borderlines (not paying regard to variations in fusion amplitude) These designations also suggest that the unphysiological values are pathological a view that might lead to interpreting this group as a transition between children with physiological (normal) phoria and those with heterotropia Such conclusions are not justified and in fact the premature and the mature fractions with unphysiological phoria were of equal size

The horizontal concomitant types of squint are all predominant in the material The distributions on eso and exo-deviations are practically identical when comparing the findings in prematures and matures Attention was focused especially on this item since according to Douglas (1960) exodeviations are more common in heterotropic children with early brain damage Nor did the present analysis demonstrate other types of squint as being specific of the premature group However this question is far from having been finally answered as the approaches had to be restricted

Among the causes of heterotropia *hereditary predisposition perinatal brain damage* and *refractive factors* (greater accommodation impulse at higher hypermetropia) are usually emphasized as being the most important ones Concerning the first and the third item it was not possible to demonstrate in the present study a greater load in the premature group in explanation of the larger number of binocular abnormalities In the case of perinatal brain damage on the other hand such a load was striking Among the prematures there was a definitely larger proportion of neurological deviants assessed neonatally as well as at follow up one year later However this could not be held responsible for the large number of heterotropias among prematures It was indeed surprising that the fraction of premature children who had been classified as deviants neurologically at the early assessments did not at the present examination exhibit a higher incidence of deviating binocular function than did premature children *without* a neurological history

On this background the *preponderance* of binocular deviations among the prematures seems to be due in some way or other to the prematurity *per se* In this connection it is natural to focus attention on the fact that an infant born several months prematurely has been using his eyes according to their purpose — to see his surroundings — relatively much longer than the full term infant in a phase where the eyes are still anatomically and functionally immature This may also without other lesions represent an obstacle to early central coordination of visual impressions a hypothesis which cannot be further approached here Only the role of low birth weight is supported directly or indirectly by the following findings

(1) When the prematurity group was divided according to the birth weight limits 1500 g and 1750 g the present binocular tests showed a tendency to a higher percentage of poor results with decreasing birth weight However this tendency was confirmed by significance calculation only in the case of one test (fusion)

(2) Heterotropia was detected already within the first year of life in 59% of

the premature squinters (n = 73) as compared with 29% of the mature squinters (n = 17)

(3) It was not possible to point out inequalities between the premature and mature group with regard to factors (hereditary predisposition social status etc) known or presumed to promote the occurrence of squint

(4) Among such established factors higher hypermetropia may be emphasized but no such relationship was apparent in a large fraction of the premature squinters

The question whether a squint has to be considered of hereditary or exogenous natur• cannot be definitely answered at our present stage of knowledge As for heredity Grützner et al (1970) have set up a model according to which squint is transmitted by multifactorial inheritance with a threshold effect To each individual the decisive factor is the combined genetic predisposition Exogenous factors — in this case the prematurity — may be imagined without knowing accurately the mechanism to cause irreversible damage *per se* or else be detrimental by lowering the named threshold

Summary and Conclusions

In a number of motor and sensory binocular tests deviations were found more often in the premature group than in the control group of mature children

Heterotropia was observed in 22 5% of the premature children (n = 302) and in 5.9% of the control group (n = 237)

Concomitant types of heterotropia were all predominant Only four children had an incomitant element In all four (all prematures) the squint could be interpreted as secondary to organic ocular changes

Cases with *small squint angles* (less than 5°) were also included in the analysis The term microtropia was not used as retinal correspondence was not considered to have been elucidated with sufficient certainty

Surgical correction of heterotropia had been performed in 9 of the 68 premature squinters but in none of the mature ones

Fusion was entirely lacking in 18 5% of the prematures (n = 270) and in 5 5% of the matures (n = 237) examined by synoptophore

Fusion amplitude was evaluated in the synoptophore in 235 premature and 191 mature children Fusion amplitudes greater than 20 pd were measured in 44% and 69% respectively distributed in both groups evenly on the ranges 20-35 pd and >35 pd

Stereopsis was lacking assessed by Wirt s principle using Titmus charts — in 16 7% of the premature (n = 300) and in 3 8% of the mature children thus examined (n = 237) For both groups the figures were higher when stereopsis was evaluated instead in the synoptophore using Chavasse slides In that case it was lacking in 24% of the premature (n = 270) and in 8% (n = 236) of the mature group

Perfect stereopsis was present in 60% of the premature (n = 300) and in 84% of the mature children (n = 237) assessed by Titmus charts With the Chavasse slides the values for both groups were about 8% lower

The *total result of the binocular tests* was that binocular vision was *not* achieved in 17 6% of the premature group (n = 301) and in 5 1% of the mature group (n = 237) Optimal binocular vision was found in 50% and 78% respectively of the two groups

In the premature group there was a significant preponderance of poor results in determination of the *near points of convergence and of accommodation*

Within the material there was no *sex difference* in the binocular status

Among the squinters – premature as well as mature – roughly one third had *squint amblyopia*

A number of *aetiological possibilities* were analysed for the purpose of explaining the appreciable excess of binocular defects in the premature group Comparisons with the mature group did not reveal skewness in hereditary predisposition social status refraction findings or in a number of pregnancy factors On the other hand early signs of central nervous system damage had been significantly more common in the premature children However the prevalence of squint was not higher in premature children with than without early neurological signs

It is concluded that the group of premature squinters may be interpreted as being composed of two parts viz the normal squinters and a special premature fraction of squinters On the basis of the clinical findings alone, it was not possible to single out specific premature types of squint However hypermetropia seems to play a relatively less important role than usual in squint materials predominated by esotropia

For want of a more concrete mechanism it seems reasonable to point out the prematurity *per se* as the main cause of the high prevalence of heterotropia among the premature group

CHAPTER 10

OPHTHALMOSCOPY

Ophthalmoscopy permits assessment of the eyeground and the refractive media If the media are blurred it is difficult to assess the fundus and sometimes only ultra sound can elucidate the morphological status of the eye In the present material this was needed in only a very few cases

The retina of the premature infant is considered to be more immature and vulnerable perinatally than in a full term infant The most violent reaction is seen in full-blown retrolental fibroplasia but the normal structural and functional dif ferentiation may be disturbed also in a less dramatic way

In the present material there were definite cases of retrolental fibroplasia but below it will be endeavoured rather to present an estimate of minor retinal damage as morphologically reflected in the ophthalmoscope

A brief review of the literature will be given as a necessary background to the present findings

Previous Findings

Ophthalmoscopic Appearances During the Neonatal Period

In *full term* infants the media are usually clear The retina is on the whole paler – in particular peripherally – and less pigmented than e g at school age The disc is pale the macula granular and the foveal reflex absent until the age of about 6 months The appearance of the adult fundus is acquired by the age of 2 years (Duke Elder 1963)

In the *premature infant* cloudy media often prevent ophthalmoscopic evaluation The vascular sheath of the lens normally disappears around the 32nd foetal week and the vitreous may show remnants of the hyaloid system or of a primary vitreous body Lastly as a link in the active phase of retrolental fibroplasia there may be vitreous clouding of exudative nature Thus ophthalmoscopy is most often com promised in the smallest prematures who are most exposed to oxygen therapy and retinal reactions Another factor which contributes to the difficulties is that dilata tion of the pupil by drugs is harder to achieve in small prematures (Carpel & Kalina 1973)

The fundus in the premature presents less differentiated than in the full term neonate (Huggert 1952 Bedrossian 1958 Rohrschneider & Meister 1962 Douglas 1969 Bulpitt & Baum 1969) The most peripheral parts of the very pale retina show no visible vessels It has been illustrated by Patz (1969) how the retinal vessels reach ever more peripherally the more normal term is approached The temporal periphery of the retina is the last part to be vascularized and it is considered to be incompletely vascularized even in full term babies As retrolental fibroplasia consists primarily in reactions in immature retinal vessels these anatomical features have afforded a kind of explanation why the temporal part of the eye is most often affected in retrolental fibroplasia and why this syndrome – or conditions morphologically indistinguishable from it – may occur also in full term infants

Retinal haemorrhage is most often encountered within the first days of life especially after deliveries with mechanical complications These haemorrhages are of approximately the same frequency in full term and in premature infants They subside in a few days and hardly leave any traces morphological or functional (Kauffman 1958 Hosaka 1963 Binch & Peretitskaya 1968 Dalsgaard & Nordentoft 1970 Pommer 1970 Barsewich & Hickl 1971 Plaanten & Schaaf 1971 Remky 1971 Sezen 1971 Szimak & Pajor 1971 Sasaki 1971 Noorden & Khodadoust 1973)

Retrolental Fibroplasia

Terry s (1942) original report of a case of full blown RLF was followed by a large number of communications on similar severe cases Owens & Owens (1949) on the other hand trying to elucidate the *initial* phases of the disease established that early signs of activity might totally regress or end in a more or less completely cica tricial stage The clinical classification which applies to this day was adopted in 1953 (editorial in the Amer J Ophthal Vol 36 pp 1333 35) At that juncture the aetiology had been clarified – retinotoxic administration of oxygen (Campbell 1951 Patz et al 1952, Kinsey 1956) – and confirmed by animal experiments (Gyllensten & Hellstrom 1952 Ashton et al 1953 Patz et al 1953 Ashton et al 1954 Ashton 1968)

The earliest sign of an *active phase* of RLF is retinal vasoreaction with dilatation and tortuosity This appearance may be extended by neovascularization retinal haemorrhage and vitreous effusion The changes are most pronounced peripherally where elevation and localized retinal detachments may occur but even such far advanced stages may regress more or less completely (Owens & Owens 1949 Reese & Stepanik 1954 Owens 1955 McNeil 1956 Gregory 1957 Alfano 1958 Kittel 1959 Baba & Hirayama 1960 Patz 1969 Baum 1971)

Cicatricial RLF is staged from I – V

Stage V is the full blown condition manifesting itself clinically as a dense grey ish membrane immediately behind the lens which is clear in the absence of compli cations

In *stage IV* the retina is partially attached but its main part is grey with cica tricial detachment This stage too means amaurosis or practical blindness

Stage III is the transition to the milder degrees The appearance is that of falciform detachment From the deformed disc a greyish retinal fold extends peripherally often in the temporal direction across the macular region Peripherally the retinal fold continues into a more extensive retinal detachment projecting to the posterior surface of the lens Central vision is greatly impaired when the macula is involved The macula may be displaced by traction (Payne & Crick 1956 Rados & Scholl 1958 Nauheim 1960 Patz & Pollack 1963 Stern & Arenberg 1969)

In *stage II* there is localized peripheral elevation of the retina thin stretched vessels and traction of the disc (dragged disc often with a pigmented half moon nasally)

Stage I is the mildest degree with a pale fundus narrowed vessels and finally myopia which is incidentally almost obligate in the various degrees of cicatricial r t olental fibroplasia.

It is evident that retrolental fibroplasia is by no means an ideal term Only stage V and partially stage IV correspond morphologically to the etymological implication of the word The more neutral expression retinopathy of prematurity is in principle preferable (Holm 1949 Ballantyne & Michaelson 1970 and others) but I have stuck to retrolental fibroplasia as it has been generally adopted in ophthalmological as well as in non-ophthalmological circles

With regard to the subsequent course of the disease it has been generally assumed that the changes run their course within the first 4 – 6 months of life However some authors have reported late complications especially in the form of retinal detachment (Johnson & Swan 1966 Tassman & Annesley 1966 Faris & Brockhurst 1969) These studies indicate that children with retrolental fibroplasia should be regularly followed not only for educational reasons (optical aids etc) but also because they may subsequently need surgical treatment

RLF Stage 0 – I ?

Finally the question may be posed whether it would be reasonable to include also a stage 0 – I I am referring to isolated occurrence of *vascular tortuosity* and/or a *pale fundus* viz ophthalmoscopic signs which are otherwise often interpreted as physiological variants

In a British material (Mushin 1971) comprising 162 prematures of a birth weight under 2000 g 7 children developed RLF stage I II despite careful control (repeated m asurements of arterial oxygen tension during treatment Roberton et al 1968 Baum & Tizard 1970 Tizard 1971) Another 11 children exhibited retinal reaction in the form of vascular tortuosity and dilatation which were found in only one out of 190 premature controls of a birth weight ≥ 2000 g Tortuo ity persisted in these cases representing (according to Mushin) minimal toxicity although arterial oxygen tension above the normal physiological levels had never been recorded in some of the cases This agrees with the result of an American follow up study (Baum 1971) of 52 adolescents (year of birth 1950 – 1953) whose birth weight had been ≤ 1500 g Among the 38 who did not have cicatricial RLF 21 had extremely marked tortu

osity the remainder milder degrees of tortuosity Baum concluded that proliferative changes of early RLF which do not progress to destructive RLF may persist as stigmata of the patients premature birth and oxygen therapy — Tortuosity has also been mentioned in previous premature series as an ophthalmoscopic finding (Gregory 1957 Alfano 1958)

As mentioned above a *pale albinoid fundus* is the general finding in the mildest degrees of cicatricial RLF This retinal appearance may be interpreted as an arrest of the usual postnatal development A pale fundus is also present in other conditions representing ocular minus variants (congenital nystagmus early high myopia etc) but on the other hand it need not necessarily represent biological inferiority a pale fundus is a well known biological variant in persons having completely normal visual function Thus it is not possible to emphasize a more specific relationship between the stated fundal appearance on the one hand and prematurity plus oxygen therapy on the other Nevertheless a relationship cannot be rejected in cases where premature children exhibit e g advanced RLF in one eye and only stage I (pale fundus etc) in the other

Speaking of the mild late sequelae there is reason to mention a publication by Faris et al (1971) These authors reported that in more than half the eyes with early active RLF regression takes place without clinically visible residual ocular damage an optimal technique of examination (cf also Watzke 1961) however usually reveals peripheral retinal changes

Summary of the Literature Reviewed Above

In a child born prematurely the coats of the eye have to pass first
opment during the postnatal period up to the status in the full term
on to the mature stage which according to opthalmoscopic
ready at pre school age It may be imagined that the retinal de
or inhibited by a number of factors, including external actions T
larly children of the lowest birth weight in part they are more
perinatally and neonatally and in part they have to pass
opment (vulnerable period) after birth In follow up studies
immature retinas will be expected in larger numbers
matures

Ophthalmoscopically the retinal findings may be
damage *Major retinal damage* comprises stages III — V of
appearances of early retinal detachment total or localized
taken to mean milder changes which morphologically *may*
variants and in which it is rarely possible to prove a more of
kind or another There may be a question of deficient de
region a pale fundus and vascular tortuosity Or else the cl
tricial RLF stages I — II or of more diffuse pigment
left by previous active lesions

The following analysis of the present results must be viewed in the light of the criteria outlined above

Present Results

Direct ophthalmoscopy was performed under *full mydriasis* Assessing the structures in the posterior pole of the eye gave rise to problems in only a very few cases in which the media were cloudy The more peripheral parts of the retina were examined with the child looking up down and to the sides

More refined diagnostic procedures were not utilized I am referring here to Goldmann s three-mirror contact lens or assessment of the peripheral retina by indirect ophthalmoscopy after local application of a scleral depressor Applying such procedures to children would require general anaesthesia and thus was flatly refused by the parents in the few cases in which it seemed indicated

Thus there was no chance of supplementing by the investigations proposed by Watzke (1961) and Faris et al (1971) The results to be reported below represent

Table 10 1 *Schematic presentation of five prematures with cicatricial retrolental fibroplasia* ("major retinal damage") listed by degree of visual handicap

The high case record numbers refer to the *original* records (see Zachau Christiansen 1972) the numbers (1 5) to the *present* case histories (see appendix)

Case rec No (present cases 1 5)	Sex	Age at examination (years)	Birth weight (grammes)	Gestational age at birth (weeks)	Neonat oxygen treatment	Stage of cicatricial RLF (left) and corresponding vis acuity (right)	
31993 (1)	♂	10	900	28?	+	V V	no light no light
51723 (2)	♀	8	1500	?	+	III III IV	3/60 0 2/60
50772 (3)	♂	10	1250	29	+	II III	6/18 1/36
50278 (4)	♀	9	1300	29	+	III I	3/60 6/18
51766 (5)	♂	9	1350	28	+	II III I?	1/60 6/12

Table 10 2 *Schematic presentation of 15 premature infants with signs indicating minor retinal damage*
Further details in case reports 6 20 (appendix)

Case rec No (Case No)	Sex	Age at exami nation (years)	Birth weight (gram mes)	Gesta tional age at birth (weeks)	Neo nat oxy-gen	Sequelae to early active retrolental fibroplasia?	Correc ted visual acuity r +l eye
12051 (6)	♂	10	1350	32	+	pre school myopia anisometropia	6/6 6/12
22688 (7)	♂	9	1950	36	+	a pigmented choroidoretinal scar temporally in left eye	6/6 6/6
30173 (8)	♂	11	1470	30	+	unilateral high myopia with albinoid retina	+ L 6/4 5
30569 (9)	♀	11	1650	31	+	pigmentary crescent on nasal side of optic disc	>6/6 <6/6
31637 (10)	♂	10	1200	28	+	pre school myopia anisometropia pallor of fundi	6/36 6/9
41732 (11)	♂	9	1400	33	+	pre school myopia anisometropia pallor of fundi	<6/6 6/6
42293 (12)	♀	9	1800	36	+	pre school myopia of left eye pallor of fundus	>6/9 <6/12
50195 (13)	♂	9	1750	31	+	pre-school myopia of left eye of fundus	6/6 1/36

Case rec. No (Case No)	Sex	Age at exami-nation (years)	Birth weight (grammes)	Gestational age at birth (weeks)	Neonat oxygen	Sequelae to early active retrolental fibroplasia?	Corrected visual acuity r+l eye
50929 (14)	♀	10	1900	32	+	pre-school myopia	<6/9 <6/9
51525 (15)	♀	9	1400	32	+	pigment changes in the left temp periphery medium tort	6/12 6/36
51573 (16)	♀	9	1200	30	+	extreme tortuosity pigment powdering in retinal periph.	>6/9 <6/6
51577 (17)	♀	9	1600	35	+	extreme tortuosity pre-school myopia, chorioret scars	6/12 6/6
51699 (18)	♂	8	1300	31	+	pre-school myopia anisometropia pallor of fundi	6/6 6/24
60385 (19)	♀	10	1450	30	+	pre school myopia narrow ret. vessels pigment scar in r e	6/9 6/6
60848 (20)	♂	9	1650	38	?	pre-school myopia	6/9 6/6

only what could be established by ordinary direct ophthalmoscopy – under otherwise optimal conditions

According to what has been discussed above divergent results were classified as major or minor retinal damage The positive findings are briefly reported in this chapter but some more details are given in the appendix

Assessment of the size of the cupping of the disc and the degree of tortuosity was not introduced as a standard item of the ophthalmoscopic evaluation until a few months after the study was started Therefore the children first examined will be excluded from the analyses concerning these parameters

Table 10.2 *Schematic presentation of 15 premature infants with signs indicating minor retinal damage*
Further details in case reports 6-20 (appendix)

Case rec No (Case No)	Sex	Age at examination (years)	Birth weight (grammes)	Gestational age at birth (weeks)	Neonat oxygen	Sequelae to early active retrolental fibroplasia?	Corrected visual acuity r + l eye
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30173 (8)	♂	11	1470	30	+	unilateral high myopia with albinoid retina	+ L 6/4.5
30569 (9)	♀	11	1650	31	+	pigmentary crescent on nasal side of optic disc	>6/6 <6/6
31637 (10)	♂	10	1200	28	+	pre school myopia anisometropia pallor of fundi	6/36 6/9
41732 (11)	♂	9	1400	33	+	pre school myopia anisometropia pallor of fundi	<6/6 6/6
42293 (12)	♀	9	1800	36	+	pre school myopia of left eye pallor of fundus	>6/9 <6/12
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30569 (9)	♀	11	1650	31	+	pigmentary crescent on nasal side of optic disc	>6/6 <6/6
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41732 (11)	♂	9	1400	33	+	pre school myopia anisometropia pallor of fundi	<6/6 6/6
42293 (12)	♀	9	1800	36	+	pre school myopia of left eye pallor of fundus	>6/9 <6/12
50195 (13)	♂	9	1750	31	+	pre school myopia of left eye pallor of fundus	6/6 1/36

Table 10 4 *Degrees of tortuosity of retinal vessels* as estimated by ophthalmoscopy in 286 children of the premature and 190 of the mature group Number of children frequencies in per cent

	Prematures n = 286	Matures n = 190
No tortuosity O	182 (63 6%)	164 (86 3%)
Slight tortuosity +	60 (21 0%)	22 (11 6%)
Medium tortuosity ++	35 (12.2%)	4 (2 1%)
Extreme tortuosity +++	9 (3 2 %)	O

(e) *Vascular tortuosity* In 286 prematures and 190 matures the ophthalmoscopic finding of tortuosity was assessed These findings were graded from 0 to +++ the latter signifying extreme tortuosity Extreme tortuosity was present in a total of 9 children all of the premature group They are briefly presented in Table 10.3 and in more detail in cases 16 17 and 21 – 27 (Appendix)

Comparison of the distribution of the various degrees of tortuosity within the premature and mature group (Table 10 4) showed a significant shift towards higher degrees of tortuosity in the prematures ($p < 0\ 01$ rank sum test)

When the premature group was divided by the birth weight limits 1500 and 1750 g the fraction of ≤ 1750 g showed at the 0 05 level significantly more pronounced tortuosity than the fraction of prematures > 1750 g The group ≤ 1500 g however had the same distribution pattern as the intermediate group of 1501 – 1750 g In other words there was among the prematures a faint tendency towards more marked tortuosity with lower birth weight but the lowest birth weight group was not particularly loaded There was no sex difference in the occurrence of tortuosity

Other Findings

Punctate retinal pigmentation was observed in 10 eyes of the premature group and in 12 eyes of the mature group

Atrophy of the optic nerve was seen in only one eye It was secondary to unilateral glaucoma in a premature boy with a Sturge Weber haemangioma (case 28)

Distorted or dragged disc was present in 5 eyes with cicatricial RLF

Conus was recorded in 4 eyes of prematures and in 2 of matures

Physiological cupping of the disc It was attemped to record the size of the

optic cup using the diameter of the disc as reference Thus assessed the prematures had large cups rather more often than the matures A total of 535 eyes in prematures and 374 in matures were studied from this point of view Just over 23% of the premature eyes had cuppings of 30% the disc diameter or more – as compared with 14% in the mature group The difference is significant also when seen in relation to individuals not only eyes The lamina cribrosa was visible in roughly 10% of the premature eyes and in 3% of the mature eyes This difference is significant at the 0 01 level

Tapetoretinal degeneration One boy of the premature group was suspected of tapetoretinal degeneration because of visual impairment, restriction of the visual field and impaired dark vision On the other hand ophthalmoscopy did not reveal signs of tapetoretinal disorder (Case 19)

Traumas In a premature boy one eye had been removed because of perforating trauma when he was 9 years of age (Case 30)

Discussion

RLF was present in 5 out of 302 children whose birth weight had been under 2000 g (1 7%) Three of these five children had reasonable practical vision (≥ 6/18 in the better eye with correction) and only two were blind In the third child with severe visual impairment (case report 31) the primary diagnosis was congenital cataract but the visual acuity was poorer than would be expected after repeated discissions The fundus could not be estimated optically because of slit hole pupils and nystagmus ultrasound examination excluded an advanced form of RLF, there were a few opacities in the vitreous but no evidence of detachment

Thus the rate of severely disabling RLF was 0 7% in the prematures of the present material It has been estimated (p 20) that the present group of surviving prematures corresponded to what would be expected from a total of almost 30 000 live births in the population – or about 40% of the annual births in Denmark On the basis of the present results therefore about 5 or 6 Danish children a year would be expected to grow blind because of RLF This corresponds approximately to the level for the period in question as stated by Seedorff (1968) she reported an incidence of severe retrolental fibroplasia of about 0 1% among *all* prematures

In this connection it may be mentioned that subsequent findings in Denmark have been largely unchanged On the basis of the notifications of children with impaired vision (Skydsgaard 1973) the annual number of new cases has not shown a definite decrease presumably because more infants in a clinically poor condition are surviving due to the extended facilities for neonatal treatment In the next few years retrolental fibroplasia will also make up the largest aetiological group among the children at the boarding school for the blind and partially sighted at Refsnæs Denmark

Incidences of severe RLF in the same range as the Danish ones have been reported by Rawls & Paulson (1966) for the state of North Carolina before and after

1953 by McDonald (1967) for those born in Britain 1950 – 1953 and by Svedbergh & Lindst.dt (1973) for Swedish children born after 1959

Tables 10 2 and 10.3 comprise the 22 premature children of the present material who had minor retinal damage and/or extreme vascular tortuosity Here we are on less solid ground with regard to diagnostic and aetiological considerations – From the diagnostic point of view we are dealing with clinical findings which when con sidered separately may be interpreted as being within the physiological range There fore my classification as "deviant" is based more upon a personal estimate than upon well-defined objective criteria Accordingly the isolated percentages given above have to be taken with some reserve Indeed the main emphasis is on com paring the two main groups this is permissible as all eyes were examined and assessed by the same person

Concerning aetiology it cannot be proved directly that the minus variants represent lesions caused by prematurity This is explained partly by the purely diagnostic considerations mentioned above but especially by the fact that the pre matures did not have routine ophthalmoscopy during the neonatal period If active RLF had been diagnosed originally the association with the present findings would have been evident However the clinical appearances of cicatricial RLF are so varied (stages I – V) that it would be unbiological not to expect transitional varieties also between stag I and normality Such a stage 0 – I could comprise the conditions emphasized in the review of the literature A pale fundus retinal pigment migrations early non hereditary myopia vascular tortuosity etc Such findings were in fact more common in the premature than in the mature group of the present materi al It is probable that at least some of these eyes represent the very mild degrees of prematurity damage

Only two of the children with extreme tortuosity (Table 10.3) are represented also in Table 10 2 (minor retinal damage) The slight overlapping of the two tables is not however at variance with Mushin s (1971) opinion that tortuosity is a sign of "minimal oxygen toxicity Tortuosity *may* be present also in the more advanced stages (stage I – III RLF) but as a rule the more pronounced the other fundal changes the more common are thin stretched vessels

It is apparent from Tables 10 1 – 10.3 that all the premature children listed fulfill the basic demands usually made on a diagnosis of RLF Low birth weight/ short gestational period and neonatal oxygen therapy However oxygen therapy cannot be adduced here as aetiological proof as during the period concerned oxygen was administered on wide indications Thus 46% of the surviving prematures of the *basic material* (upper birth weight limit here the usual 2500 g) received supplementary oxygen and of course this percentage was higher for the present premature group whose birth weight was below 2000 g Among them 74% received oxygen in the incubator and a few additional ones oxygen by funnel Around 1960 the general practice in the obstetric units was that infants of a low birth weight were placed in an incubator for a short time because of their smallness and expected starting dif ficulties At that time 40% oxygen in the incubator was regarded as the safe upper limit and out of regard to the eyes this limit was not exceeded (restrictive oxygen therapy cf p 15)

The opinion to-day is as already emphasized that *any* supplementary administration of oxygen involves a risk of toxic endothelial damage to immature retinal vessels, hyperoxygenation will result if the premature infant is not actually suffering from hypoxia On this background it is striking that my premature group – including so many risk cases – does not contain more cases of definite (major damage) or possible (minor damage) retinal oxygen damage than it does The explanation is probably that in actual fact the oxygen therapy was administered with the utmost reserve *As soon as permitted by the infant s condition the oxygen was levelled off* and discontinued (This is also reflected by the data on oxygen therapy given in the case reports in the Appendix)

Summary and Conclusions

Among the 302 children of the present material whose birth weight was less than 2000 g five had cicatricial retrolental fibroplasia Two of these five were blind i e 0 7% of the total Three cases were abortive and had entailed no major visual disablement

Signs of minor retinal damage – interpreted as the sequelae to early action upon the retina – were more common among the premature children than among those of the mature control group This points to the existence of stage 0 – I RLF

High degrees of vascular tortuosity and of physiological cupping of the disc were significantly more common in the premature than in the mature group

However the great majority of eyes at risk – low birth weight combined with neonatal oxygen therapy – exhibited no actual ophthalmoscopic signs of damage at follow-up

CHAPTER 11

LENS

First a brief outline of the literature Definitions of congenital cataract and the incidence of this condition will be discussed on the basis of reported materials Moreover the concept "cataract of prematurity and some factors relating to the foetal vascular systems of the eye will be elucidated

Previous Findings

Congenital Cataract Definitions and Materials

Cataract designates opacities of the lens and/or lens capsule Lenticular opacities occur in nearly all neonates (Seissiger 1929) somewhat older children (Pellaton 1923 Stocklin 1957) and young adults (Bellows 1945) Most of these opacities however are of no clinical significance They are easily overlooked in routine examinations in which attention is focused primarily on what clearly differs from that which the examiner feels is physiological (non pathological)

The term congenital cataract is generally not used for such negligible opacities but reserved for cases of grossly demonstrable changes of the lens usually associated with some degree of visual impairment Problems of definition – apart from the above morphological aspect – also attach to the time at onset of the abnormality A number of the cases normally included in materials of children with congenital cataract do not manifest themselves clinically until several months after birth and are thus not in the true sense congenital (François 1959 Brown 1963 Nordmann 1966 Murphy et al 1967)

However the greatest variations in the composition of the published materials are due to the functional aspects *Materials of blindness* (a) of course comprise the heaviest cases while *hospital materials* (b) also include cases with a favourable prognosis *Population surveys* contain also cases so mild as to cause no major visual impairment and therefore not referred to eye clinics for treatment These differences in recruiting are of course reflected in the results

(a) Congenital cataract is responsible for an appreciable number of the cases in

the *materials of blindness* in children and adolescents Fraser & Friedman (1967) found congenital cataract in 13 5% of 776 British children with a severe visual handi cap born during the period 1941 – 1962 In a number of series reviewed by François (1959) congenital cataract was listed as the main diagnosis in 10–30%

(b) *Hospital series* are composed of children referred because the cataract has been estimated as being actually or potentially disabling The size and composition of such materials are influenced on the one hand by geographic and social factors on the other hand by iatrogenic conditions meaning capacity in surgical technique current attitude to indications etc Children with congenital cataract have made up 1/4 – 1/2 per cent of all patients in several eye departments (Prudhommeaux & Reverse 1962 Riddel 1962 Liesmaa 1972)

(c) Estimates on the prevalence of early-onset cataract in the *population* may be based partly upon calculations from hospital materials compared with population size and birth rate partly on screening of sections of the population The latter is difficult to practice as it would require very large random samples owing to the rare occurrence of the condition

A cautious estimate based upon Brændstrup s (1943) findings indicates that 0 02 – 0 03 per cent of Danish children born around 1930 had to be admitted for operation because of early (non traumatic congenital or infantile) cataract In Fin land the rate seems somewhat lower (0 01%) according to Liesmaa s (1972) analysis of the births from the 1950 s McDonald (1967) estimated 0 04% of British children For New South Wales Harley & Hertzberg (1965) reported 10 new cases a year in a population of several millions

François (1959) reported a fairly high prevalence among newborns viz 0 4% This value is based upon a study by Chace et al (1950) who found cataract in 4 out of 1 024 examined during the first week of life The summary description of these cataracts is restricted to 'polar type which presumably means a mild form which hardly has called for surgery It is possible therefore that in fact the incidence was 0 according to the criteria applying to the above hospital series

Seissiger (1929) in the slit lamp examination of 500 newborns found no cases of classical congenital cataract but often mild opacities of the lens as also men tioned above Frandsen (1960) in her squint study did not look particularly for lenticular changes However she recorded 4 cases of non traumatic cataract in the approx 10 000 children from regular school and one case among the almost 2 000 children who were being taught as mental defectives Engbæk (1970) among 1 765 Danish school children aged 7 found one – incidentally unilateral – case of cataract

According to the named publications it seems reasonable to estimate the pre valence of clinically significant cataract in children as being 2 – 5 cases in 10 000

Cataract of Prematurity

In a number of *cases of early* cataract the aetiology can be established Some cases are hereditary Other known causes are maternal viral infections during pregnancy metabolic disturbances certain systemic diseases and congenital malformations

These factors will not be discussed further here, the interested reader is referred to reviews by e.g. François (1959) Harley & Hertzberg (1965) and Menn & Crawford (1971).

In our context more interest attaches to the fairly large proportion of all materials that *cannot* be classified aetiologically Among such cases premature birth is strikingly common and the concept *cataract of prematurity* has to some extent been adopted This is supported on the publications which are collected in Tables 11 1 and 11.2 plus a number of case reports (Liebman 1955 François 1959 Babel 1960

Table 11 1 *Frequency of early cataract* (congenital and probably also infantile cases included) *in some premature series*
Birth weight (BW) limits and numbers of infants

	Follow up examinations of premature infants Birth weight limits and number		Frequency of early cataract Number or percentage	
Eames (1946)	BW <2500 g (Full term controls)	n = 155 n = 439)		0 [illegible] (0 5%)
Hess & Lundeen (1949)	BW <1260 g	n = 216	5 cases	2 3%
Guy (1954)	BW <2500 g	n = 1000	3 cases	0 3%
Castren (1955)	BW <2000 g BW 2000 2500 g (Full-term controls)	n = 109 n = 371 n = 217)	2 cases 1 case 0	[illegible]
Ryan (1956)	BW <1600 g	n = 430	[illegible]	
Brown (1963)	[illegible]	[illegible]	[illegible]	
McDonald (19[illegible]7)	[illegible]	[illegible]	[illegible]	[illegible]
Möller (1970)	[illegible]	[illegible]	[illegible]	

Table 11 2 *Frequency of prematurity in some congenital cataract materials* comprising predominantly the subgroups of *unknown aetiology*

	Classification of materials or subgroups	Incidence of prematurity
Bronge Hagberg & Molin (1960)	19 cases with prenatal factors"	12 prematures (63%)
Harley & Hertzberg (1965)	59 cases of unknown aetiology"	21 prematures 19 of whom had *birth weights be* low 2000 g (36%)
Fraser & Friedman (1967)	77 non hereditary cases	32 with prematurity and/or perinatal difficulties (42%)
Merin & Crawford (1971)	(a) 79 cases with convulsive dis order or other central nervous system involvement (a) 106 cases of unknown aetiology"	(a) 41 prematures (52%) (b) 19 prematures (18%)
Liesmaa (1972)	152 cases - 19 of which however *had ectopic lenses and not pri-marily cataract*	22 prematures *(17% according to* author s text

Ziegler 1960 Nordmann 1966) All these have been cases of permanent cataract, transient cataracts in small prematures have been reported by McCormick (1968) and Normann et al (1970)

Fraser & Friedman (1967) considered the common occurrence of cataract in prematures to be one link in a perinatal damage syndrome in infants of low birth weight Schaffer (1969) in Adler s Textbook of Ophthalmology used the term cataract of prematurity applying to that part of the congenital cataracts in which no other aetiology but the prematurity seemed likely Such eyes were said to have as a rule no *other* abnormalities

The incidences of cataract of prematurity and of RLF are both so low that co-incidence of the two must be statistically very rare Accordingly a 3% incidence of cataract in children with RLF (Reese & Stepanik 1954) is relatively high Nearly all the cases were of typical complicated cataract Cataract in RLF develops mainly in those eyes which exhibit the most severe trophic morphological changes

From around the 6th foetal month atrophy of the vascular sheath of the lens sets in and blood flow through the hyaloid artery ceases The result of this involution is that in the newborn infant there are normally only negligible remnants of the foetal vascular systems although such slight vestiges are very common (Seissiger 1929) Further regression takes place during the first months of life

If birth occurs several months before term the involution of the vascular sheath is of course less advanced at the time of birth this is part of the explanation why the media are blurred in prematures A reasonable assumption appears to be that normal regression is disturbed or delayed by the violent actions to which the newborn is exposed at too early a transition to extrauterine conditions of life Indeed it was originally believed by Terry (1942) that the new disease entity which was later to be named retrolental fibroplasia was due to pathological reactions in persisting foetal vascular systems

A certain reaction to oxygen therapy has subsequently been described in a con vincing manner by Hornblass (1971) He hoped thereby to have demonstrated a convenient clinical parameter by which to guide the dose of oxygen to small prema ture infants However such a possibility has not been confirmed by later clinical studies This may be – at least partially – because of the difficulty involved by performing a satisfactory slit-lamp examination of prematures in a poor condition in an incubator

François (1959) summed up materials in which filiform remnants of the pu pillary membranes were present in 8% to 26% of normal children and adults Among residua on the posterior surface of the lens "hyaloid corpuscles ('Mittendorf's dot" or "cataracta polaris posterior spuria" – at the site of insertion of the hyaloid artery) have been reported as a physiological finding in about 10% (Vogt 1919 Berliner 1949 Stocklin 1957) Vogt s "Bogenlinie was found in more than just over half the children of Stocklin s material

Present Findings

The examinations were carried out under cycloplegia with a Haag-Streit slit lamp with standard oculars x 10 and magnification x 1 or x 1 6

All 237 full term children were examined The original group of prematures numbered 302 but 30 had to be subtracted as they were examined in their homes Moreover, it was not reasonable to make any statement concerning the lens (trau matic cataract?) in the eye which had been removed after a perforating trauma Thus a slit lamp evaluation was made of 543 eyes in 272 children of the premature group and of all 474 eyes in the mature group

Positive findings were recorded in 11 prematures and 2 matures Table 11 3 presents schematically the various lens findings while further information is given in the Appendix (cases 1 4 5 and 31 – 40) Lastly for the sake of another case should be mentioned viz that of the premature child

Table 11 3 *Lens findings at slit lamp examination* of 272 children from the premature and 237 from the mature group
Schematic presentation of positive findings and reference to the case reports (appendix)

	Premature group n = 272	Mature group n = 237
Complete cataracts	*Case 31* BW 1150 g Classical" bilateral congenital cataract now secondary cataract after surgery *Case 1* BW 900 g (twin) Dense complicated cataracts in eyes with cicatricial RLF	
Partial cataracts	*Case 4* BW 1300 g Circumscribed cloudy opacities bilaterally and lens coloboma in one eye only Cicatricial RLF *Case 5* BW 1350 g Circumscribed peripheral cataract in one eye only Cicatricial RLF	*Case 32* BW 3500 g Partly fusiform cataract localized anteriorly in one eye only
Coerulean cataracts	*Case 33* BW 2100 g (twin) *Case 34* BW 1900 g (twin) *Case 35* BW 1800 g (twin) *Case 36* BW 1850 g	
False (?) posterior cataracts (Mittendorf's dot)	*Case 37* BW 1700 g Central annular opacity unilat *Case 38* BW 1700 g Flat opacity centrally in one eye only *Case 39* BW 1700 g Paracentral white dot in one eye only	*Case 40* BW 3250 g Central annular opacity unilaterally

genital cataract (case 41) who had not been included in the present material because of a primary recording error (p 23)

A pupillary membrane persisted – in the form of filaments crossing the anterior

surface of the lens – in 20 (7 4%) of the prematures examined and in 29 (12 2%) of the mature children The difference is not significant at the 0 05 level (χ^2 test) In roughly one third of the named cases with persisting residua the finding was positive in both eyes in the remainder unilateral

Within the premature group it was not possible to demonstrate a correlation between birth weight and persisting pupillary membrane In particular there was no evidence that such residua were more common in the children of the lowest birth weight

There was not in any case with lens changes a family history to indicate heredity

Discussion

In this fraction of the total study there was no intention to describe the morphology of the lens in detail As positive findings I recorded only cases having lens changes so marked that I assessed them primarily as being beyond the physiological limits Drawing such a limit is of course arbitrary

A distinction was made between the *gross* and the *microscopic* changes Thus it applies to the cases listed in Table 11.3 as complete and partial cataracts that the opacities were grossly visible when assessed with a torch or ophthalmoscope Such cataracts would have been diagnosed if present also in the 30 premature children examined in their homes i e without a slit lamp at disposal It is justified to conclude therefore that true (= gross) cataract occurred in 4 (1.3%) of the 302 children of the premature group and in one (0 4%) of the 237 mature children

In one of the four *gross* cases in prematures there was dense complicating cataract in both eyes combined with stage V RLF Retrolental fibroplasia was present also in another two of these four prematures but less severe (abortive forms) These were cases in which the prematurity had entailed retinal changes and in which the moderate lenticular opacities may have been of the same aetiology

In the last one of the four children it is difficult to tell whether there may also have been RLF changes This was not indicated by opthalmological examination at the age of 4 weeks according to which the "media were clear and ophthalmoscopic appearances normal" Cataract was recorded a few months later manifesting itself clinically as typical congenital cataract – and repeated discissions were carried out already during early childhood

Surgery was not even considered in the case of the other patient with gross cataract The partial cataracts did not present any significant optical hindrance and surgery would have made no sense at all in the amaurotic child with retrolental fibroplasia and phthisic eyes From a therapeutic point of view – assessed on the basis of lens morphology – there was then cataract requiring treatment in only two of the premature children (0 7%) although operation could be considered in only one of them There was no case of cataract requiring treatment in the mature control group

The present findings may be fitted into the picture afforded by Table 11 1 In papers where this aspect is elucidated the criteria have been greatly doubtful cataract

On the other hand the studies listed in the table differ mutually in their birth weight limits If nevertheless all series of the table as well as the present material are considered together there are – after exclusion of Brown s (1963) 17 cases (because of unstated size of the series) – a total of 28 cases of cataract among 4 290 prematures This is a total incidence of just over 0 6% (or 65/10 000) to be compared with the estimated frequency in the population (2 – 5/10 000 children cf p 172) However the collected premature group is not representative of a truly premature population On the one hand there is an overrepresentation of the low birth weight classes On the other hand some cases of cataract must be lacking from that fraction of prematures who have died before follow up On the whole however it must be justified to estimate the incidence of cataract as being considerably higher among prematures than among a section of the population in the same age groups (It must be borne in mind also that prematures are included in the populations on which the above population estimate is based)

All considered the present material contributes to interpreting cataract of prematurity as a separate aetiological group

Filifrom remnants of the pupillary membrane were observed in almost 10% of all the children This is in reasonable conformity with previous findings It was not possible to demonstrate any association between birth weight and persistent pupillary membrane, in particular the premature group was not loaded in this respect Indeed there have not been other materials to definitely indicate an increased frequency of persisting remnants of foetal vessels in premature children To a certain extent this is in keeping with the pathogenetic mechanisms Retrolental fibroplasia is a sequel to an action upon developing retinal vessels The vascular sheath on the other hand is a system in involution at the time that the exogenous action sets in

Summary and Conclusions

Grossly visible cataract was present in 1 3% of the children of the premature group (4 out of 302) and in 0 4% of those of the mature group (1 out of 237) A hereditary basis could not be demonstrated

In the *one case of the mature control group* there was a question of unilateral partial cataract Accordingly the difference between the two main groups is relatively greater if the incidence is calculated per number of eyes (1 2 and 0 2% respectively) instead of individuals with positive findings

The four cases in prematures One child had classical congenital cataract on both sides Another child had complete dense cataract on both sides and full-blown retrolental fibroplasia as well Two children had partial cataract – unilateral and bilateral respectively – co-existing with abortive retrolental fibroplasia

Only two of the five children with gross cataract had major optical hindrance i e indication for surgery on the basis of the lens morphology Thus *cataract requiring treatment* was present in 0 6% of the premature children and in no case of the mature group

The 302 children of the premature group represent 90% of the prematures who

– judging by the data of the basic material – were known or suspected to be alive in spite of the low birth weight (< 2000 g). Let it be mentioned, for the sake of completeness, that among the 10% who did not attend there was one known case of cataract; this child was not included in the present analysis.

The present material supports the concept "cataract of prematurity" as denoting cases in which no other aetiology is known. When considering also the relevant literature it seems to be established that cataract is more common among prematures than among children of the general population.

A persistent pupillary membrane was found in almost 10% of the children examined, but not more often among prematures than matures.

From the findings it is also apparent that the predominant majority of the present children did not have significant lenticular changes.

CHAPTER 12

OCULAR MALFORMATIONS ADDITIONAL OCULAR FINDINGS

Villumsen (1970) analysed the occurrence of congenital malformations in the infants and foetuses of the 9 006 pregnancies which made up the basic material He used the definition of McKeown & Record (1960) that a congenital malformation is "A macroscopic abnormality of structure attributable to faulty development and present at birth"

According to Villumsen (1970) the basic material included only one infant with congenital malformation of the eye a premature boy with bilateral cataract diag nosed at the age of 9 days Paradoxically this is the very case which was *not* included in the present ocular material because of a recording error (cf p 23)

Present Findings

In the above text and tables several references have been made already to the case reports in the appendix

Table 12 1 briefly lists the various malformations recorded in the ophthalmological examination of the 539 children who made up the present material 22 malformations were distributed on 20 children all without evidence of an hereditary basis Eight had malformations of the eye proper the remainder of the ocular adnexa The malformations were relatively more common among the prematures (5% of 302 children) than among the matures (2% of 237)

Congenital ptosis was observed in nine cases bilateral in eight However the ptosis was secondary in two of the children both premature In these cases it was just one factor in major syndromes (a) retrolental fibroplasia with amaurosis (Case 1 App) and (b) "encephalopathy muscular dystrophy which had been diagnosed in a boy having – among other signs – retroflexion of the head, however some levator function was present The remaining seven cases were mild with preserved levator function and no visual hindrance In several cases surgical treatment had been discussed earlier but not carried into effect

Table 12 1 *Congenital malformations of the eye and ocular adnexa* in the premature and mature group
Number of children and type of lesion
The case numbers refer to the reports of the appendix

		Prematures n = 302	Matures n = 237	Remarks
Malformations of the eye	Congenital (?) cataract	4	1	see chapter 11 Cases 1 4,5 31 and 32
	Colobomas	2		(a) typical unilateral iris coloboma (b) unilateral lens coloboma case 4
	Vascular malformations	1		conjunctival and episcleral haemangiomas - as part of a Sturge Weber "naevus flammeus" case 28
Malformations in the ocular adnexa	Congenital ptosis	6	3	further details in the text
	Coloboma of eyelid	1		4 x 2 mm notch of upper lid unilaterally case no 12
	Distichiasis	1		a double row of eyelashes in both upper lids
	Calcified epithelioma (Malherbe)	1		tumour removed from the upper eyelid at 6 years Traumatic origin?
	Haemangioma of the skin	1	1	(a) the above mentioned case 28 with Sturge Weber haemangioma (b) a full term girl with a 5x5 mm capillary haemangioma on the upper eyelid

Discussion

Some of the conditions listed in Table 12 1 are no doubt congenital but without having been recorded at the examinations during the neonatal period Similar experience has been made in other series in which "many minor conditions and most intraocular anomalies are unremarked (Duke Elder 1964) The malformations given in the table are on the whole so slight as to escape detection in the examination of the newborn infant whose eyes often still bear the marks of the Credé prophylaxis

Another decisive item however is that some of the cases in Table 12 1 may conceivably not have been manifest at birth Let me refer to Chapter 11 in which it was discussed whether the cases of cataract were to be interpreted as postnatal or congenital This discussion is topical also but with an opposed sign in dealing with the sequelae to retrolental fibroplasia This condition may leave lesions morphologically exactly like e g congenital falciform retinal detachment or certain retinal colobomas This is of particular importance in pre RLF materials in which such findings during childhood would inevitably be classified as congenital

Additional Ocular Findings

Restriction of ocular motility and *manifest nystagmus* (4 prematures cases 1 3 5 and 31) *corneal dystrophy* (case report 1) and *vitreous changes* (cases 1 and 31 (established by ultrasonography) and 3 and 10) were found in only a few of the prematures but often combined and together with other signs of severe ocular disease *Latent nystagmus* or *nystagmus on gaze deviation* from the primary position were observed in another 6 children all prematures (5 of whom are *described in case* reports 3 4 15 19 and 21) There was no case of *well-defined selective pareses of the external eye muscles* *Corneal abnormality* had been present in yet another boy of the premature group (case 30) due to traumatic perforation *of the eyeball* the eye had been enucleated immediately after the accident

The distribution of the various *eye colours* did not show essential differences between the premature and mature group *Most of the* children had light irides comprising the colours grey greyish blue greenish and blue Dark eyes (brown irides) were seen in 11% of the premature *and in 11 4%* of the mature children A side difference (anisochromia) was observed in one premature and in two mature children There was no instance of heterochromia

In one publication (Bassin & Skerlj *1937) it has been* claimed that eyes having light irides are biologically inferior to dark eyes This could not be confirmed in the present material The distributions of *refractive* values visual acuity axial length measurements and binocular vision *within the main* groups (prematures and matures) showed no relation to the colour of the iris

Colour sense defects Twenty six *children* (with good vision) could not manage the Ishihara plates Most of *these cases* were typical deuteranomalies Another 6 children of the material failed at this test either in one or both eyes but because of severe visual impairment

The 26 colour blind children were distributed in conformity with the most common inheritance (sex linked recessive) there being 22 boys (8 4%) and 4 girls (1 4%), the incidence was the same in the premature and mature group Twelve of the 26 children viz 10 boys and 2 girls had a positive family history In 8 of the 10 *boys* the maternal grandfather and/or brothers had defective colour vision in the last two boys the paternal grandfather and a maternal uncle respectively In the two *girls* the known hereditary predisposition seemed to be from the father one of them also had a sister with anomalous colour vision

Actual family studies or further tests of colour vision were not carried out On the basis of the data it is not possible to elucidate in more detail the inherited or acquired nature of the colour vision defects

Summary and Conclusions

In 5% of the premature and 2% of the mature children malformations of the eyes and/or ocular adnexa were observed These cases were predominantly very mild and of no functional importance except in two premature children one of whom had congenital cataract and the other infantile glaucoma in association with a congenital Sturge Weber haemangioma

These ocular malformations had not been recorded at the paediatric examination during the neonatal period It is briefly discussed whether some of the malformations generally described as congenital do in fact not manifest themselves until postnatally

Restricted ocular motility nystagmus corneal and vitreous changes were ob served in only a very small number of children, usually combined and together with more generalized ocular stigmatization All these children belonged to the premature group

There was no difference between the premature and mature group in iris colour or colour vision anomalies

CHAPTER 13

MULTIPLE PREGNANCY

Below the ocular status in the 81 children born of multiple pregnancies will be discussed from two aspects (a) Comparison within matched pairs (b) comparisons between the group of children of multiple and single pregnancies.

The object of analysing the matched pairs was to assess the influence of the lower birth weight. A background is formed int. al by the twin studies of Babson et al (1964) and Churchill (1965) which demonstrated delayed somatic and intellectual development in the child with the lower birth weight

During intrauterine life the children of a multiple pregnancy have been exposed to the same maternal and exogenous actions, and several – monozygotic – have exactly the same genetic pattern. Therefore differences at follow up within pairs of multiple birth can be related to e.g differences in birth weight which is of interest in our context Under such circumstances the effect of low birth weight can manifest itself even in the small series that are obtainable when using the criterion multiple – Indeed it was due to the wish of analysing such matched pairs that the present premature group includes a few children whose birth weight had been ⩾ the upper weight limit of 2000 g (a total of 17 children having a surviving co-twin or co tripl t *below* this weight limit)

Comparison of the single and multiple-born prematures was done *to ascertain* whether these groups develop differently From the obstetrical point of view the multiple-born infants are considered a special risk group, delivery *often occurs before* term, and the less favourable presentations are *common This results* in higher morbidity and mortality – cf int al a number of series reviewed by Zachau Christiansen (1972)

Present Findings

The 81 multiple-borns make up 27% *of the premature group*, distributed on 75 twins and 6 triplets There were 29 *intact (= surviving)* pairs of twins and two sets of intact triplets As to the remaining 17 twins the co twin had died before the time of follow-up the majority during the neonatal period

Grouping into monozygotic and dizygotic pairs would have been preferable but the data did not permit such a distinction with sufficient certainty The basic material had not been systematically tested for this factor and was in particular insufficient concerning the tissue and blood group criteria which to-day ought to be fulfilled in twin studies (Schiottz Christensen 1972) The compromise was to include *all surviving multiple-birth pairs of the same sex* viz 22 pairs of twins and two pairs from each set of triplets

Among these 24 pairs the results for the one having the lower birth weight were compared with those for the heavier child Table 13 1 therefore depicts *the possible*

Table 13 1 *Mean values of some extraocular and ocular parameters in 24 pairs of multiple birth children of the same sex* (top) and in the subgroup (bottom) of twelve pairs who had ultrasound oculometry The children with *lower birth weight* (within the pairs) are compared with their *higher birth weight matches*

		Lower birth weight children	Higher birth weight children
Data for the whole group of 24 pairs	Height (cm)	140 7	140 9
	Skull circumference (cm)	52 3	52 8
	Interpupillary distance (mm)	57 5	57 4
	Binocular visual acuity (Snellen 6/6 = 1 0)	1 14	1 17
	Refraction (dioptres)	+ 1 12	+ 0 99
Data for the twelve pairs who had ultrasound oculometry	Refraction (dioptres)	+ 1 20	+ 1 14
	Corneal curvature radius (mm)	7 56	7 69
	Ocular axial length (mm)	22 8	23 2
	Anterior chamber depth (mm)	3 9	4 0
	Lens thickness (mm)	3 6	3 6
	Vitreous length (mm)	15 3	15 6

influence of a lower birth weight within the pairs. By virtue of the selection differences in gestational period and sex may be disregarded So can the role of birth order In 13 of the 24 pairs the firstborn was of the lower birth weight while in the remaining 11 pairs this was reversed The mean difference in birth weight within the pairs was just below 300 g

The upper half of Table 13 1 lists the mean values of a number of parameters in the 24 pairs (height circumference of skull interpupillary distance binocular visual acuity converted into decimal fraction cycloplegic refraction stated as the mean of both eyes) Its lower half, in the same way gives the values for a number of refractive parameters (refractive value corneal curvature radius and axial ultrasonic measurements) in those of the pairs (12 in all) in whom both had been subjected to ultrasonic oculometry

It is apparent from the table that the mean values for the two groups are close together There is a faint tendency towards smaller body and ocular proportions in the group having the lower birth weight especially with regard to the features of prematurity lower values for axial length and corneal radius of curvature (cf Chap-

Table 13.2 *Comparison of some data from the group of premature single birth and of premature multiple birth children* Mean values and standard deviations Oculometry and keratometry were not performed in all cases Actual number and results

	Premature infants of single birth n = 221		Premature infants of multiple birth n = 81	
Birth weight (g)	1625	± 252	1767	± 334
Age at examination (years)	10 25	± 0 95	10 31	± 0 94
Height (cm)	137 2	± 8 1	137 4	± 8 4
Refraction (D) in right eye	+0 59	± 2 15	+1 11	± 1 04
in left eye	+0 73	± 1 73	+0 90	± 2 26
Measurements of right eyes (mm)	(n = 146)		(n = 45)	
Axial length	23 02	± 1 03	22 98	± 0 76
Ant chamber depth	3 80	± 0 24	3 88	± 0 26
Lens thickness	3 62	± 0 21	3 63	± 0 21
Vitreous length	15 60	± 0 97	15 47	± 0 94
	(n = 200)		(n = 69)	
Corneal curvature radius (mm)	7 67	± 0 30	7 69	± 0 24

ter 6) However the p values were insignificant for all compared parameters (using Wilcoxon s matched pairs signed rank test as well as parametric t test in cases where it was reasonable to use) The extent of disc cupping and the degree of tortuosity at ophthalmoscopy also did not differ significantly and the same result was found in analysing binocular function (sign test)

The total conclusion then, is that within the pairs it was not possible to demon strate significant differences in ocular status according to higher/lower birth weight It must be borne in mind however, that the limited size of the material has pre sumably contributed to the inability of tendencies (premature size and functional deficit in the child of lower birth weight) to manifest themselves in the significance calculations

Comparisons of Prematures of Single and of Multiple Births

Table 13 2 presents the mean values of a number of extraocular and ocular para meters *in the two groups of prematures (birth weight height age refractive values,* axial ultrasonic measurements and corneal radius of curvature) The results for both groups are fairly similar except for birth weight and refractive values which were relatively higher in the group of multiple births

The distribution of refractive values is apparent from Table 13.3 which demon strates a slight shift towards hypermetropia in the children of multiple pregnancies This shift is significant (rank sum test) also when the calculations are based upon number of individuals instead of number of eyes

Table 13 3 *Refraction values* in single eyes in the premature group subdivided ac cording to *single or multiple birth*
Frequencies (in per cent) in one-dioptre refraction classes

	Prematures of single birth n = 440 eyes	Prematures of multiple birth n = 162 eyes
+4 0 D and higher	2 3%	1 3%
+3 0 +3 9 D	3 9%	3 7%
+2 0 +2 9 D	5 7%	14 8%
+1 0 +1 9 D	38 2%	42 0%
O +0 9 D	35 2%	29 0%
-0 1 -1 0 D	6 1%	8 0%
-1 1 -2 0 D	3 6%	0 6%
-2 1 -3 0 D	1 4%	
-3 1 -4 0 D	1 6%	
Myopia exceeding 4 0 D	2 0%	0 6%

Table 13.4 *Corrected binocular and monocular visual acuity* in the premature group subdivided according *to single or multiple birth*. Frequencies in per cent

	Corrected binocular visual acuity in prematures of		Corrected monocular visual acuity in prematures of	
	single birth n = 221	multiple birth n = 81	single birth n = 442 eyes	multiple birth n = 162 eyes
6/4.5 and > 6/6	62.5%	53.1%	46.1%	34.5%
≦6/6	26.2%	39.5%	34.0%	43.2%
≷6/9	8.1%	6.2%	11.5%	16.1%
≦6/12	3.2%	1.2%	8.4%	6.2%

Table 13.5 Some states of *binocular motor balance and sensory function* (Titmus stereopsis) in prematures *of single and of multiple birth*. Clinical findings classified as in Tables 9.5 and 9.11. Frequencies in per cent

		Prematures of single birth n = 220	Prematures of multiple birth n = 80
Binocular motor balance	Orthophoria	13.6%	22.5%
	Physiological heterophoria	52.9%	40.0%
	Unphysiological heterophoria	12.7%	10.0%
	Heterotropia	20.8%	27.5%
Stereoptic visual capacity (titmus)	Good stereopsis	63.2%	52.5%
	Medium stereopsis	12.7%	13.7%
	Poor stereopsis	7.3%	17.5%
	No stereopsis	16.8%	16.3%

Table 13 4 sets out, roughly the distribution of the binocular and monocular visual acuity in the two groups which did not differ significantly (rank sum test) Among the multiple birth children however somewhat fewer eyes belonged to the most optimal visual acuity group (χ^2 test $p < 0\ 05$) but in the case of the binocular visual acuities the difference is insignificant

Binocular functions are illustrated in Table 13 5 A relatively larger number of children with heterotropia and relatively fewer with optimal stereopsis were recorded among the multiple birth children but the differences between the two groups are not significant

A number of other clinical parameters were tested with the same negative result Apart from the distribution of refractive values then the ocular status of the multiple birth prematures did not differ from that of the single birth prematures

Discussion

The twin studies of Babson et al (1964) and of Churchill (1965) showed within the pair a delayed somatic and intellectual development in the child having the lower birth weight In analogy an influence upon the ocular status might be expected but analysis of the 24 pairs of multiple birth children of the same sex from the present material did not afford significant evidence thereof However it has been emphasized already that the material does not permit definite conclusions In part too few pairs were available and in part it was not possible to single out definitely monozygotic pairs which are preferable in such paired assessments

According to the data obtained the group of surviving multiple birth children (n = 81) did not exhibit major signs of functional or size deficit as compared with the group of single birth prematures (n = 221) Thus the increased obstetrical risk to the group of multiple births did not manifest itself at the present follow up examination about the age of 10 years

In the present grouping of the prematures however the higher mean birth weight for the multiple birth children is striking Indeed they were also less premature than those of single birth judging by the gestational periods available for about two thirds of the children The mean period was 34 5 weeks for the multiple and 33 weeks for the single births In this respect therefore the two groups are not ideally comparable Accordingly it may be maintained that – by virtue of a more favourable gestational period and birth weight – the multiple birth prematures ought to have differed positively from the single birth prematures in ocular status Positively is taken to mean approaching the results in the mature group However this factor is not considered of such importance that it could reasonably entail changes or modifications of the conclusions to which certain reservations apply already

Summary and Conclusions

Among the surviving pairs of multiple birth children of the same sex it was not possible to demonstrate significant differences in ocular status in relation to the higher/lower birth weight within the pair From the ocular point of view the group of multiple birth prematures was in broad features like that of single birth pre matures and on the basis of the data obtained it is not reasonable to distinguish between the premature" and the multiple trauma No specific ocular lesions were found in children born of multiple pregnancies

CHAPTER 14

OCULAR FINDINGS IN RELATION TO SOME OBSTETRICAL PAEDIATRIC DATA

Chapter 2 described in detail the present *ocular* material and the *basic* material whence it was recruited The reason for choosing the named basic material (rather than random samples of the population) was the available wide assortment of uniformly elucidated data Owing to these data the findings of the ophthalmological study could be related to a number of obstetrical and paediatric findings

Above the data from the basic material have been used partly for assessing the comparability of the two main groups partly for analysing the possible influence of various risk factors upon the eye This has applied especially to whether differences in ocular status between the main groups could be due to factors other than the prematurity *per se*

At this site I shall give merely a summary account of some factors concerning pregnancy and the first year of life referring for further particulars to the previous chapters in which these aspects have been discussed already

Factors Concerning Pregnancy

Social status Judging by (1) the mother s marital status at delivery and (2) a social grouping into classes I – V there was no significant difference in the composition of the premature and mature group (cf Chapter 2)

Within the same two main groups there was no significant relationship between social status on the one hand and refraction findings and visual acuities on the other but heterotropia was significantly more common among children of a lower social class (IV + V) than among those of the higher social strata (I + II + III) In the low social classes the percentile height was also lower (Chapter 7) but only among the children of the mature group Among the prematures the mean percentile height proved to be entirely unrelated to social factors It is possible that the "normal" relationship has been masked by a stronger influence by low birth weight/short gestational period

Maternal proteinuria Proteinuria was of approximately the same frequency in both main groups (10% in the premature and 6% in the mature group mothers)

There was no significant relationship between maternal proteinuria and the child s ophthalmic performance in the tests (judging by visual acuities refractive findings and binocular vision)

Maternal anaemia Anaemia was rather more common among the mothers of the mature children (30%) than among those of the prematures (19%) but within both groups this condition had exerted no influence upon the children s subsequent ocular status

Maternal blood groups and sensitization The maternal blood groups were of the same distribution in both main groups Sensitization (Rh ABO or others) had been recorded in 8 mothers of the premature and in 2 of the mature group

Maternal smoking during pregnancy Smoking was more common and heavier among the mothers of the premature children than of the mature ones 17% and 10% respectively had been smoking more than 10 cigarettes daily whereas the values for non-smokers (0 – 2 cigarettes daily) were 42% and 63% in the two groups The difference between the smoking pattern in the two groups of mothers is highly significant

In the case of both main groups the mean birth weight was 50 g higher for the fraction having non-smoking mothers than for children whose mothers had smoked more than 10 cigarettes daily

Maternal smoking did not have any demonstrable influence upon the total distributions of refractive values binocular vision or visual acuities

Single or multiple pregnancy This has been discussed separately in Chapter 13 27% of the children in the premature group were of multiple birth but this showed no essential influence upon the ocular status at follow up

Factors Concerning the Child

Asphyxia had been significantly more common among the children of the premature than of the mature group (Table 9 17 p 153) Within the two groups the subsequently recorded ocular status in the children who had been asphyctic did not differ significantly from that in the non asphyctic ones However signs of asphyxia had been rather more common among prematures with than in prematures without myopia ($p < 0\ 05$)

Neonatal jaundice 31% of the prematures and 5% of the matures had had clinically moderately severe or severe jaundice and serum bilirubin exceeded 15 mg/100 ml in 34% and 1% respectively Levels above 20 mg/100 ml had been found in a total of 32 prematures (12%) and in 2 matures (0 8%) – Exchange transfusion had been carried out in 5 premature and 5 mature infants

It was not possible to demonstrate a relationship between the severity of jaundice on the one hand and the ocular status (visual acuity refraction, and binocul vision) on the other

Oxygen therapy About 80% of the prematures had received a supplem

though "restrictive", of oxygen in some way or other (predominantly in the incubator, cf also Chapter 10). In the control group of matures this rate was 5%. Supplementary oxygen had in most cases been administered for only a few hours, in some cases for a few days.

Retrolental fibroplasia was diagnosed in a total of 5 prematures who were discussed in more detail in Chapter 10. Incidentally, it was not possible to demonstrate within the two main groups any significant differences in ocular status according to ± oxygen therapy. (This item was not further explored because of the somewhat undifferentiated information available from the punch cards of the basic material.)

Central Nervous System Damage

(a) *Judging By the Data from the Basic Material.* Let me refer again to Table 9.17 in the chapter on binocularity. This table showed how often brain damage was estimated to be present in the paediatric assessment during the first week of life and at the follow-up one year later. Signs of brain damage were recorded in almost every fourth premature infant, but in only a few of the mature group. In other words the premature group was distinctly more loaded than the mature group, but apparently this has not manifested itself in the current ocular status. In particular it might have been expected to find a higher incidence of heterotropia in the fraction of children with neurological damage than in the others, but this was not so. Visual acuity and refraction also failed to exhibit any relation to the initial classification of the children as normal or neurologically deviant.

These results must be viewed on the background of the difficulties in the early neurological assessment of an infant (Zachau-Christiansen 1972). It would therefore be desirable to supplement by more recent findings, but the children of the ocular material had not been subjected to systematic neurological follow-up.

(b) *Judging By the Present Findings.* To some extent the present data allow such a supplementary evaluation. The parents were systematically questioned about difficulties of behaviour, especially in relation to the school situation. As "educational deviants" I recorded children who were unable to manage in regular school in spite of extra lessons and other help (i.e. children transferred to special schools or classes for retarded children, class repeaters, etc.). The information given on this item must therefore be considered fairly reliable, although no attempt was made to corroborate it by psychotechnical tests, school testimonials, etc.

According to these data 26% of the premature group were "educational deviants" (78/302) as compared with roughly 8% of the mature group (20/237). Deviants were significantly more common among the premature boys than among the premature girls (31% and 21% respectively, $p < 0.05$). The distribution on the birth weight groups was the same for the groups of normal prematures and "educationally deviant" prematures, about 30% of both being in the birth weight group ≤ 1500 g. Among the deviants the share of multiple births (17/78) was similar to that in the total premature group (27%). Among the 78 deviants three had a severe visual

Table 14 1 *Schematic presentation of 21 children with obvious brain damage* subdivided into 12 cases with spastic cerebral palsy (top) and cases with other cerebral disorders (bottom) The case numbers in the ophthalmic column refer to the appendix

Case rec No	Sex	Birth weight (g)	Able to attend normal school	Central nervous system diagnosis	Ophthalmic findings
30080	♂	1550	no	paraplegia	
30785	♂	1200	yes	paraplegia	Case 22 (hyper metropia reduced stereops)
30803	♂	1500	yes	paraplegia	Exophoria (tropia ?) reduced stereopsis
30964	♀	1050	no	paraplegia (mono ?)	
31431	♀	1550	yes	hemiplegia	
31602	♂	1350	yes	paraplegia (?)	Case 24 (extreme tortuosity)
50772	♂	1250	yes	paraplegia	Case 3 (RLF 6/18 esotropia nystagmus)
51766	♂	1350	yes	paraplegia	Case 5 (RLF + early myopia no stereopsis)
60307	♂	1600	no	paraplegia	Exotropia gross stereopsis only
60385	♀	1450	no	tetraplegia	Case 19 (early myopia esotropia)
60395	♂	1850	no	monoplegia (?)	Exotropia reduced stereopsis
60560	♀	1450	no	paraplegia	Esotropia no stereopsis

Case rec No	Sex	Birth weight (g)	Able to attend normal school	Central nervous system diagnosis	Ophthalmic findings
30059	♀	1700	no	sequelae to encephalitis at the age of 7	Case 21 Esotropia (since birth) no stereopsis
30160	♀	1500	yes	epilepsy (phenytoin)	
31300	♂	1800	no	epilepsy? severe behav disord	Gross stereopsis only
31984	♂	1800	no	dystonia musc deform "organic brain damage"	Ptosis abn head post gross stereopsis only
50101 A	♂	1950	no	cong encephalopathy mental deficiency	Small angle esotropia
50101 B	♂	2100	no	idem	Small angle esotropia
51577	♀	1600	no	infantile neurosis encephalopathy	Case 17 (early myopia reduced stereops)
60456	♀	1800	no	hydrocephalus (Spitz Holter op)	Exotropia no stereopsis
62082	♂	1550	no	mental deficiency	Gross stereopsis only

(B) Visual Disablement in the Premature Group

The literature on the sequelae to prematurity is characterized to some extent by the most severe and most disabling syndromes within the ophthalmological as well as the paediatric neurological field In contradistinction the present premature group may be considered *representative* – by virtue of a high tracing and follow up rate On this basis it is possible to state the incidence of the various ocular problems (including also the minor ones) in prematures and assess their significance

(1) *Blindness was observed in 1%* of the children in the premature group This frequency must be considered relatively high compared with that in the general population On the other hand it is low when compared with the frequency of blindness in series of prematures from the early years of oxygen therapy

(2) This fairly favourable impression still applies when assessing the *ophthalmological handicap in the remaining 99%* of the premature group The deviations were only exceptionally disabling *per se* Thus all 99% were considered capable of standing up to the demands of regular school from the *visual* point of view (with corrected visual acuity $\geqslant 6/18$) In the long run however the increased incidence of *binocularity disturbances* among the prematures may influence the subsequent choice of occupation and similarly squint amblyopia is tantamount to a poorer visual reserve On the other hand a squint is rarely a real handicap in the course of education

(C) The 'Trauma of Prematurity"

The surplus of ophthalmologically deviant conditions in the premature group is interpreted as a consequence of the *prematurity per se* It was not possible to arrive at supplementary explanations neither on the basis of heredity nor in the assessment of a large number of adverse perinatal factors In other words the eyes have exhibited less possibility of optimal development and function when the violent change of environment at birth has taken place an appreciable time before term – The lowest birth weight classes appear to be particularly at risk

(D) Practical Consequences of the Study

The most important practical consequences of the present study are

(1) The main prophylactic measure is still *to prevent the occurrence of retrolental fibroplasia* In general then there is a question of measures which (a) reduce the frequency of premature birth and (b) secure an optimal obstetrical paediatric service in connection with birth and neonatal period – This should include regular ophthalmological follow-up of oxygen treated prematures within at least the first months of life

(2) For prematures of a low birth weight (e g below the present selected limit of 2000 g) *annual ophthalmological follow-up* is recommended This is based partly

upon knowledge concerning the greatly increased risk of ophthalmological defects (severe as well as mild) partly upon the wish for *early therapeutic measures* (prophylaxis against amblyopia in cases of squint and anisometropia correction of myopia of prematurity and other major refractive anomalies, social/educational measures in cases of isolated visual defect and of visual impairment combined with other handicaps) – Considering the limited number of children in the lowest birth weight classes such *routine* ophthalmological examinations during pre school age ought to be practicable at least in countries with a good medical service

The four items A to D may be summed up briefly as follows

Premature children who have been of low birth weight exhibit more often than mature children a *deviant ocular status* judging by a number of functional and morphological criteria

Apart from the few cases of blindness the ophthalmological defects must be considered predominantly mild where the functional aspects are concerned On the basis of an isolated assessment of the ocular findings it is estimated that 98 99% of the children in the present premature group have a possibility of fending for themselves without special ophthalmological measures (apart from ordinary glass correction and the like)

The *prematurity per se is held responsible* for the increased number of ophthalmological defects in the group of prematurely born children – The lowest birth weight classes seem to be particularly at risk

Prematures of a low birth weight must be considered to be ophthalmologically on the whole a group at risk Therefore routine *prophylactic measures* should be carried through not only during the *neonatal period* but throughout childhood The important measures are amblyopia prophylaxis and glass correction besides the more general optical-educational aspects

SUMMARY

(The outline of each chapter closes with a synopsis emphasizing mainly the present results)

Introduction The background and object of the study are briefly stated *By establishing the ocular status in a group of children around the age of 10 years it was endeavoured to assess the overall influence of prematurity (low birth weight) upon the subsequent development and function of the eyes*

Chapter 1 *General features of premature series reported during the past half century* are reviewed emphasizing primarily the significance of birth weight limits especially when selected lower than the 2500 g on which the current definition of prematurity is based Then follows a survey of what may be called from the therapeutic point of view the four epochs of prematurology referring chiefly to the varying principles of oxygen therapy during the neonatal period The relationship to damage to the eyes and central nervous system is discussed

In view of the often marked differences in birth weight limits neonatal service etc between the published materials of prematures the importance of suited control groups is emphasized

Chapter 2 The present ophthalmological study is based upon a *prospective paediatric investigation in the University of Copenhagen 1959-61 called the basic material* For 9 006 consecutive pregnancies in the Maternity Units of the University Hospital a number of uniformly assessed data were available Some were related to the results of the present ophthalmological follow-up study performed about 10 years later

The present ophthalmological material consists of a premature group (n = 302) of surviving children whose birth weight had been < 2000 g The full term control group also selected from the basic material by birth weight criteria *comprises 237 children whose birth weight had been 3 – 4 kg* The two groups are considered truly comparable Owing to a high tracing rate (90% and 74% of the stipulated premature and mature group respectively) it was possible to obtain a representative picture of both groups

In the analysis the results were divided into (a) motor and (b) sensory

(a) *Heterotropia* (manifest squint) was observed in 22 5% of the premature children (n = 302) and in 5 9% of the control group (n = 237) The latter percentage corresponds approximately to that in the general population in the age range con cerned

Within both groups about one third of the children with heterotropia had squint amblyopia

Concomitant squint was the predominant type There were no cases of purely paralytic squint

Nine (out of 68) premature squinters but none of the mature group had had surgical correction

(b) *Fusion* was entirely lacking in 18 5% of the prematures examined by syn optophore (n = 270) and in 5 5% of the control group (n = 237) Fusional amplitudes exceeding 20 prism dioptres were significantly more common among the mature than among the premature children

Stereopsis was absent in 16 7% of the prematures (n = 300) and in 3 8% of the matures (n = 237) when assessed on the basis of Titmus charts With the Chavasse slides in the synoptophore these values were somewhat higher (24% and 8% re spectively) Perfect (foveal) stereopsis was significantly more often found in the mature than in the premature children so examined

In the tests for the near points of convergence and accommodation the prema ture group also did significantly worse than the mature group

At the paediatric assessment during the first year of life the children of the premature group had been classified essentially more often than the mature children as having central nervous system damage These rates corresponded accurately to the percentages of heterotropia However the children initially deemed to be neurologi cal deviants did not squint more often than the children (within the same main group) who had been considered as having no cerebral damage

Prematurity as such is held responsible for the higher frequency of binocular disturbance in the prematures

Chapter 10 *The ophthalmoscopic findings during the neonatal period* are described (review of literature) with a special view to the development of abnormalities (in particular *retrolental fibroplasia*)

A diagnosis of RLF was made in 5 out of the 302 premature children Two cases were stage V and had resulted in blindness whereas three were abortive with only minor visual handicap

Various signs of minor retinal damage were more common among the pre mature than among the mature children In some of the prematures fairly high degrees of *tortuosity* may persist as a sequel to active retrolental fibroplasia

Most of the eyes at risk (low birth weight combined with oxygen therapy) presented as ophthalmoscopically normal at follow up

Chapter 11 On the basis of the literature the author discusses (a) the prevalence of *congenital and infantile cataract* in the population (estimated as 2 – 5 cases in

10 000) (b) the concept "cataract of prematurity and (c) persistent *remnants of the hyaloid vascular system.* The classification of cataract as congenital is discussed on the basis of morphological chronological and visual criteria

In the present material 13 children had *changes of the lens* of them 11 were prematures Grossly visible cataract was present in 4 prematures (including three with RLF) and one mature child An hereditary basis could not be demonstrated in any case

When added to the findings in the literature the present material supports the justification of the concept cataract of prematurity

Chapter 12 deals with *ocular malformations.* Malformations were found in 5% of the premature and in 2% of the mature children All are tabulated (Table 12 1) Loss of vision had occurred in only two cases (a) a premature child with congenital cataract and (b) a premature child with Sturge Weber haemangioma and ipsilateral glaucoma

A number of ocular conditions encountered in the material are briefly discussed Pareses of ocular muscles nystagmus corneal and vitreal changes occurred in a very small number of (premature) children predominantly included in the syndromes mentioned in the preceding chapters There was no difference between the prema ture and mature group in iris colour or colour vision anomalies

Chapter 13 27% of the 302 premature children were of *multiple pregnancies* none of the control group To increase the possibility of paired comparisons of multiple birth children 17 children of a birth weight ≥ the upper limit *(2000 g)* were *included* in the present premature group all 17 had a surviving co-twin or co *triplet of a birth* weight below this limit

Analysis of 24 multiple birth pairs of the same sex *did not* disclose significant differences in ocular status bearing relation to the higher/lower birth weight within the pair

Ophthalmologically the group of multiple birth children was largely like the group of single birth prematures In other words *the increased* obstetrical risk of multiple birth did not leave its marks on the ocular status of the survivors

Chapter 14 It was analysed whether *it was* possible to demonstrate among the children of the ophthalmological material *special risk groups on the basis of the data from the basic material concerning (a) pregnancy and (b) the first year of life* These factors were (a) social status maternal proteinuria and anaemia blood groups and sensitization smoking and (b) asphyxia neonatal jaundice oxygen therapy and signs of central nervous system damage *during* the first year of life

None of these conditions assessed separately seemed to affect the total ocular status judging by the visual acuity refractive values or binocularity findings

Lastly brief mention is made of the children who were estimated on the basis of their history and behaviour at the ophthalmological examination as having *brain damage or being merely educational deviants* There was a significant preponder

ance of such cases in the premature group Thus a severe cerebral handicap was essentially more common than severe visual disablement among the prematures

Chapter 15 *The closing remarks supply condensed answers to the questions posed in the introduction* The present ophthalmological material showed that

– Premature children whose birth weight has been low exhibit more often than mature children a deviant ocular status judging by a number of functional and morphological criteria

– One per cent of the premature children were blind Otherwise the premature group showed predominantly reasonable or good ocular function judging by the demands of school and society upon the visual organ

– Prematurity *per se* is held responsible for the increased number of ophthalmic defects in the group of premature children The lowest birth weight classes proved to be particularly at risk

– Owing to the higher frequency of abnormalities – severe as well as mild – the premature group must definitely be considered a group at risk, also from the ocular point of view Therefore routine prophylactic measures are indicated not only during the neonatal period but throughout childhood

SUMMARY IN DANISH

DANSK RESUME

(Efter hvert kapitel er anført et sammendrag med hovedvægten lagt på egne resultater)

Indledning Baggrunden for og formålet med arbejdet trækkes kort op *Gennem en fastlæggelse af øjenstatus hos en gruppe børn omkring 10-års alderen tilstræbes en samlet vurdering af indflydelsen af præmaturitet (lav fødselsvægt) på øjnenes senere udvikling og funktion.*

Kapitel 1 Der gives *en belysning af generelle træk vedrørende præmaturmaterialer* fra det sidste halve århundrede Først fremhæves betydningen af fødselsvægtgrænser især hvor sådanne er valgt lavere end de 2500 gram den gængse præmaturitetsdefinition er baseret på Dernæst gives en oversigt over hvad man terapeutisk set kan benævne præmaturologiens fire epoker primært med henvisning til de vekslende principper for iltbehandling i neonatalperioden Relationen til læsioner af øjne og centralnervesystem diskuteres

Med baggrund i forskellige præmaturmaterialers ofte betydende forskelle i fødselsvægtgrænser neonatal service m.m fremhæves betydningen af egnede kontrol grupper

Kapitel 2 Det foreliggende arbejde er et sideskud til et *prospektivt pædiatrisk studie fra Københavns Universitet 1959-61 Dette betegnes udgangsmaterialet* For ialt 9 006 konsekutive svangerskaber fra Rigshospitalets fødeafdelinger foreligger en række ensartet oplyste data hvoraf nogle er sat i relation til resultaterne af den aktuelle oftalmologiske efterundersøgelse

Øjenmaterialet består af en præmaturgruppe (n = 302) af overlevende børn med fødselsvægt < 2000 gram. Den fuldbårne kontrolgruppe er ligeledes udvalgt fra udgangsmaterialet efter fødselsvægtkriterier og består af *237 børn med fødselsvægt mellem 3 og 4 kg* Komparabiliteten mellem de to grupper anses for virkelig god Det har gennem en høj opsporingsprocent (henholdsvis 90 og 74 procent af de stipulerede præmatur og maturgrupper) været muligt at tegne et repræsentativt billede af de to grupper

Kapitel 3 og 4 *omhandler de valgte undersøgelsesmetoder og statistiske beregnings principper* Der er lagt særlig vægt på gennemgangen af de *aksiale okulære ultralyd målinger*

Kapitel 5 En indledende litteraturgennemgang belyser *dels det normale refraktions mønsters ændringer under barndom og opvækst dels den særlige præmatur-myopi* som er beskrevet af flere forfattere — både med og uden relation til retrolental fibroplasi (RLF)

Refraktionsværdierne viste for såvel præmatur som maturgruppe den fra andre arbejder velkendte leptokurtose omkring en let hypermetrop gennemsnitsværdi (+ 0 75 for præmature og + 1 07 D for mature) samt skewness mod myopi

Præmaturgruppen viste kun en let forskydning mod myopi i forhold til de mature børn, henholdsvis 13.3 og 9.3 procent af de indgående øjne var myope

De præmatures relative overvægt af myopi synes at bero på en særlig fraktion af øjne med tidlig (før skole) myopi som anses for en følge af selve præmatuntеten For 27 af 80 myope præmature øjne (eller 4 5 procent af den totale præmaturgrup pes øjne) var myopien konstateret *tidligt* i barndommen, dette var kun tilfældet for ét af maturgruppens 44 myope øjne

Indenfor præmaturgruppen viste den laveste fødselsvægtgruppe (≤ 1500 gram) den største afvigelse fra de matures refraktionsnorm

Det foreliggende materiale støtter opfattelsen af en myopia of prematurity'

Kapitel 6 *Tilvæksten i øjenstørrelse under barndom og opvækst belyses* gennem en række oculometriske arbejder som på baggrund af markante indbyrdes forskelle især på det måletekniske område viser overraskende god overensstemmelse For flertallet af øjne synes længdevæksten afsluttet allerede før puberteten

Resultater af ultralydoculometri foreld for højre-øje (i cykloplegi) fra ialt 191 præmature og 159 mature børn Det gennemsnitlige præmature øje udviste et stør relsesdeficit på omkring 0 3 mm for *akselængde og glaslegemestrækning* og på 0 18 mm for *den corneale krumningsradius* Kammerdybder og aksiale linsetykkelser var næsten ens i de to grupper tendensen gik i retning af relativt fladere kamre og tykkere linser hos de præmature

For det *emmetrope* øje blev gennemsnitsværdierne 23 1 mm og 23 5 mm for akselængden og 7 67 mm og 7 85 mm for den corneale krumningsradius i begge tilfælde med de præmatures værdier nævnt først

Maturitetsforskellen var af samme størrelsesorden som kønsforskellen i tenalet De præmatures øjne forholdt sig oculometrisk til de matures som pigers til drenges

Øjnene med *før skole myopi* havde kortere akse og krummere corneae end ventet efter refraktionsværdierne Bortset fra denne lille præmature fraktion de optiske komponenters kovariation upåvirket af præmatuntеten

Det klassiske dogme at 1 mm ændring i akselængde ækvivalerer med 3 refraktionsændring kan ikke med rimelighed opretholdes Dette baseres på såvel foreliggende resultater som på arbejder fra litteraturen

Kapitel 7 Gennemsnitsværdier for *legemshøjde kranieomfang og interpupillar distance* var for de præmature signifikant mindre end for de mature børn Der forelå således – jævnsides med det okulære – et mere generelt præmaturt størrelsesdeficit Dette lader sig ikke forklare kronologisk ud fra de faktiske forskelle i konceptionsalder som gør de præmature 1½ til 2 måneder yngre end angivet af deres fødselsdato

Det kan på det foreliggende ikke fastslås hvorvidt det drejer sig om *blivende størrelsesdeficit eller om blot forsinket udvikling* – Øjet følger udviklingsmæssigt det cerebrale vækstmønster det vil sige med kraftig vækst i de første 2 3 leveår men derefter kun ganske beskeden årlig tilvækst Specielt anses cornea for tidligt færdig vokset Den *corneale tværdiameter* fandtes i den foreliggende præmaturgruppe signifikant mindre end i kontrolgruppen af mature børn Dette kan tale for et blivende præmaturt størrelsesdeficit i hvert fald for øjnenes vedkommende på samme måde som det af konsforskellen betingede er det

Også *exophthalmometriværdier* var mindre hos de præmature Dette forkaster en ældre hypotese om at præmature børn også efter de første levemåneder hyppigere skulle frembyde øget okulær protrusion

Der fantes en vis sammenhæng mellem de forskellige analyserede okulære og ekstraokulære vækstparametre men ikke med refraktionsværdierne

Kapitel 8 omhandler *synsstyrkeforhold.* Først gives en litteraturoversigt til belysning af synsstyrkefund i børneårene dels generelt og d ls m d relation til præmaturitet

1 procent af den foreliggende præmaturgruppes børn måtte betegnes som *blinde* (to med retrolental fibroplasi en med congenit cataract) Risikoen for blindhed i gruppen er hermed fundet væsentligt højere end den for børnepopulationen skønnede risiko – Rest n af præmaturgruppen (99 procent) og hele maturgruppen havde med optimal korrektion 6/18 eller bedre

Beregnet på basis af antal *øjne* blev de tilsvarende hyppigheder som følger 96 2 procent af de præmatures øjne og 98 5 procent af de matures øjne kunne bringes til at se 6/18 eller derover

De præmature børn udviste indenfor den mere optimale del af synsstyrkeskalaen en signifikant forskydning mod lavere (mindre optimale) værdier i forhold til de mature børn Dette gjaldt såvel de binokulært som de monokulært bestemte synsbrøker (med optimal korrektion) Indenfor præmaturgruppen var fraktionen med laveste fødselsvægt (≤ 1500 gram) dårligere placeret end resten af gruppen En særlig lav placering indtog undergruppen af præmature med før-skole myopi Dette i modsætning til de øvrige myope børn som efter korrektion ikke udskilte sig negativt

Kapitel 9 omhandler *binokularitetsforhold.*

Nogle punkter med relation til den foreliggende problemstilling belyses i den indledende litteraturgennemgang 1) Hyppigheden af skelen i normalbefolkningen 2) Hyppigheden af skelen blandt præmature 3) Hyppigheden af præmaturitet i skele materialer 4) Skelen centralnervesystemslæsioner og præmaturitet 5) Fordelingen mellem eso og exodeviationer

De anvendte undersogelsesmetoder og dıagnostıske knterıer meddeles og dıs kuteres

Resultaterne er ved opgørelsen ınddelt ı de a) motonske og b) sensonske

a) *Heterotropı* (manıfest skelen) forelå hos 22 5 procent af de præmature børn (n = 302) og hos 5 9 procent ı kontrolgruppen (n = 237) Det sıdste svarer nogenlunde tıl hyppıgheden ı befolknıngen på det pågældende alderstrın

I begge grupper var der skeleamblyopı hos ca 1/3 af bornene med heterotropı

Konkomıterende skeletyper domınerede ganske Der var ıngen tılfælde af ren paralytısk skelen

9 (ud af 68) præmature skelebørn var opereret for deres stıllıngsanomalı men ıngen ı maturgruppen

b) *Fusıon* manglede helt hos 18 5 procent af de synoptoforundersøgte præma ture (n = 270) og hos 5 5 procent ı kontrolgruppen (n = 237) Fusıonsbredder bedre end 20 pd forelå sıgnıfikant hyppıgere hos de mature end hos de præmature børn

Stereopsıs manglede helt hos 16 7 procent af de præmature (n = 300) og hos 3 8 procent af de mature børn (n = 237) ved bedømmelsen med Tıtmus tavler Med Chavasseslıdes ı synoptofor blev tallene lıdt højere (24 og 8 procent henholdsvıs) Perfekt (foveal) stereopsıs forelå sıgnıfikant hyppıgere blandt de undersøgte mature børn end ı præmaturgruppen

Præmaturgruppen havde også ved konvergens og akkommodatıonsnærpunktbe stemmelse sıgnıfikant dårlıgere resultater end de mature børn

Præmaturgruppens børn var ved den pædıatrıske vurderıng ı første leveår væsent lıgt hyppıgere bedømt som CNS læderede end de mature børn og hyppıghederne svarede procentısk nøje tıl heterotropıforekomsterne De ınıtıalt neurologısk af vıgende børn skelede ımıdlertıd ıkke hyppıgere end de børn (ındenfor samme hoved gruppe) som blev anset for cerebralt ubelastede

Præmatunteten som sådan holdes ansvarlıg for den højere skelehyppıghed hos de præmature

Kapıtel 10 *Det oftalmoskopıske bıllede ı neonatalperıoden* belyses med særlıgt hen blık på udvıklıngen af patologıske tılstande (ısær *retrolental fibroplasi)*

Hos ıalt 5 af materıalets 302 præmature børn stılledes dıagnosen RLF To tıl fælde var komplette med blındhed, tre var abortıve uden væsentlıg synshındrıng

Forskellıge holdepunkter for *mınor retınal damage* fandtes hyppıgere ı præma turgruppen end hos de mature børn Højere grader af *tortuosıtas* kan formentlıg hos en del præmature persıstere som en følge efter aktıv retrolental fibroplası

De fleste øjne at rısk (lav fødselsvægt kombıneret med ıltbehandlıng) frem trådte ved efterundersøgelsen som oftalmoskopısk normale

Kapıtel 11 Ud fra lıtteraturen belyses a) Hyppıgheden af *congenıt og ınfantıl cataract* ı befolknıngen (anslået tıl 2 5 tılfælde pr 10 000) b) Begrebet *'præmatur-cataract'* og c) Persısterende *rester af det hyaloıde karsystem.* Klassıficerıng som congenıt cataract dıskuteres ud fra morfologıske tıds og synsmæssıge knterıer

I det forelıggende materıale beskrıves ıalt 13 børn med *lınseforandrınger* heraf de 11 præmature Makroskopısk synlıg cataract var tıl stede hos 4 præmature (heraf

de tre med retrolental fibroplasi) og et maturt barn Hereditær basis kunne i intet tilfælde påvises

Materialet kan sammen med den foreliggende litteratur støtte berettigelsen af begrebet præmatur-cataract

Kapitel 12 omhandler *malformationer i øjenregionen.* Misdannelser blev beskrevet hos 5 procent af de præmature og hos 2 procent af de mature børn Samtlige er angivet i skemaform (tabel 12 1) *Kun i to tilfælde var der tale om synstab* a) et præmaturt barn med congenit cataract b) et præmaturt barn med Sturge Weber hæmangiom og glaukom på det pågældende øje

Der redegøres i ovrigt summarisk for en række okulære tilstande beskrevet i materialet Øjenmuskelpareser nystagmus cornea og glaslegemeforandringer optrådte hos et kun ganske begrænset antal (præmature) børn og her helt overvejende som led i sygdomsbilleder omtalt i de foregående kapitler Der var ingen forskel mellem præmatur og maturgruppe hvad angik irisfarve og farvesynsanomalier

Kapitel 13 27 procent af præmaturgruppens 302 børn var ud af *flerfold svangerskab* Samtlige kontrolgruppens børn var enbårne For at øge mulighederne for parvise sammenligninger af flerfold fødte inkluderedes i præmaturgruppen ialt 17 børn med fødselsvægt ≥ den ellers gældende øvre fødselsvægtgrænse i materialet (2000 gram) alle 17 havde en overlevende medtvilling eller trilling med fødselsvægt herunder

Der kunne ved analyse af 24 flerfold fødte enskønnede par ikke demonstreres signifikante forskelle i øjenstatus med relation til højest/lavest fødselsvægt indenfor parret

Gruppen af flerfold fødte forholdt sig øjenmæssigt i store træk ligesom gruppen af enbårne præmature Den øgede obstetriske risiko ved flerfold fødsel markeredes altså ikke hos de overlevende i den senere øjenstatus

Kapitel 14 Kapitlet er en analyse af hvorvidt der indenfor øjenmaterialets børn kunne påvises *særlige risikogrupper på baggrund af de fra udgangsmaterialet forelig gende oplysninger om a) svangerskab og b) barnets første leveår* Det drejede sig om a) sociale faktorer maternel proteinuri og anæmi blodtyper og sensibilisering tobaksforbrug og b) asfyksi neonatal ikterus iltbehandling samt tegn på centralnervesystemslæsioner indenfor første leveår

Ingen af disse tilstande syntes vurderet hver for sig at belaste den samlede øjenstatus bedømt ud fra synsstyrkefund refraktionsværdier og binokularitetsforhold i materialet

Afsluttende gives en *kort omtale af de børn* som bedømt ud fra anamnese og adfærd ved øjenundersøgelsen skønnedes direkte *hjerneskadede eller blot skole defekte* Præmaturgruppen havde en signifikant overvægt af sådanne tilfælde svære cerebrale handikap forelå blandt de præmature væsentligt hyppigere end svær visuel invaliditet

Kapitel 15 *I de afsluttende kommentarer gives et sammenfattende svar på de spørgsmål som er formuleret i indledningen.* Det foreligg nde øjenmateriale har vist

— Præmature bom med lav fødselsvægt frembyder oftere end mature bom afvigende øjenstatus bedømt ud fra en række funktionelle og morfologiske kriterier

— Én procent af præmaturgruppens bom var blinde I øvrigt viste præmatur gruppen sig oftalmologisk set helt overvejende rimeligt eller godt fungerende bedømt ud fra de skole og samfundsmæssige krav til synsorganet

— Præmaturiteten som sådan holdes ansvarlig for det øgede antal oftalmo logiske defekttilstande i gruppen af for tidligt fødte børn De laveste fødselsvægt klasser har vist sig i særlig grad at risk

— Den højere forekomst af oftalmologiske afvigelser — svære såvel som lette — understreger at præmaturgruppen afgjort må betragtes som en risikogruppe også okulært set Rutinemæssige profylaktiske foranstaltninger bør derfor gennemføres ikke blot i neonatalperioden men gennem hele barndommen

REFERENCES

Abeloos E (1970) Amétropies et inspection médicale scolaire Bull. Soc belge Ophtal. *154* 443-448

Alfano J.E (1958) Myopia of prematurity Amer.J Ophtal. *46* 45-49

Alm I (1953) The long term prognosis for prematurely born children. A follow-up study of 999 premature boys in wedlock and of 1002 controls. Acta paediat Uppsala *42* suppl. *94*

van Alphen, G W.H.M (1961) On emmetropia and ametropia. Ophthalmologica suppl. ad vol. *142* Karger Basel.

Andersen B (1971) Biostatistikkens grundbegreber – Nogle statistiske metoder In Pedersen, J & *Havsteen B* ed (1971) Lægevidenskabelig forskning *pp* 86 156 F.A.D L. *København* Århus, Odense

Andrée G (1964) Zur Entwicklung der foveolaren Fixation Ber dtsch. ophthal. Ges. *66* 271 273

Ashton N Ward B & Serpell G (1953) Role of oxygen in the genesis of retrolental fibroplasia preliminary report. Brit.J Ophthal. *37* 513 520

Ashton N Ward B & Serpell, G (1954) Role of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. Brit.J Ophthal. *38* 397-432

Ashton N (1968) *Donder's lecture Some aspects of the comparative pathology of oxygen* toxicity in the retina Brit.J Ophthal. *52* 502 530

Baba K & Hirayama M (1960) Comparative study of congenital retinal fold and retrolental fibroplasia. Paediat Univ Tokyo *5* 1 2 Ref from Zbl. ges. Ophthal. 1961-62 *84* 303

Babel J (1960) Cataractes *post natales précoces a évolution rapide* Étude de quatre cas. Arch. Ophtal Paris, *20* 146 153

Babson S G Kangas, J Young N & Bramhall, J.L. (1964) Growth and development of twins of dissimilar size at birth Pediatrics, 33 327 333

Ballantyne A.J & Michaelson I C (1970) Textbook of the fundus of the eye sec ed p 254 Livingstone Edingburgh and London

Barsewich B & Hickl, E.J (1971) Retinablutungen bei Neugeborenen. Klin.Mbl Augenheilk. 159 121

Bassin R & Skerlj B (1937) Augenfehler und Augenfarbe Klin Mbl. Augenheilk *98* 314 321

Baum J.D & Tizard J P.M (1970) Retrolental fibroplasia Management of oxygen therapy Brit med Bull. *26* 171 174

Baum J D (1971) Retinal photography in premature infants forme fruste retrolental fibroplasia Proc roy.Soc.Med sect Ophthal. *64* 777 779

Baum J.D (1971) Retinal artery tortuosity in ex premature infants Arch. Dis Childh *46* 247 251

Bechetoille A & Saraux H (1970) Biométrie oculaire ultrasonique Étude de 100 yeux appartenant a une population homogène jeune Ann Oculist *203* 131 149

Bedrossian E H (1958) The eye A clinical and basic science book pp 211 218 Thomas Spring field

Bellows J (1945) Frequency and location of punctate opacities in three hundrede young crystalline lenses Arch Opthhal. Chicago *33* 229 236

Bender L (1964) Brain damage in blind children with retrolental fibroplasia. Trans amer neurol. Ass. *89* 183 184

Berliner M L (1949) Biomicroscopy of the eye pp 1024 1031 Hoeber New York

Beskow B (1949) Mental disturbances in premature children at school age Acta paed Uppsala *37* 125 149

Betsch A (1929) Über die menschliche Refraktionskurve Klin Mbl. Augenheilk *82* 365 379

Biering-Sørensen K Florander J Jensen J & Sigsgaard J (1962) Late prognosis for prema tures. Acta paediat scand suppl. *140* 113 114

Birge H.L (1956) Myopia caused by prematurity Amer.J Ophthal. *41* 292 298

Birch T V & Peretitskaya V.N (1968) Organ of vision in children with retinal haemorrhage sustained in the neonatal period Vestn Oftal. /4 23 27 Ref from Excerpta med Ophthal. 1969

Blaszó S & Giesel, V (1971) Correlation between strabismus and central nervous system injuries. J ped Ophthal. *8* 18 22

Blegen S.D (1953) The premature child The incidence aetiology mortality and the fate of the survivors. Acta Paediat. Uppsala *42* suppl. 88

Botman L (1932) Hematropin and atropin cycloplegia A comparative study Arch. Ophthal. Chicago 7 389 398

Brander T (1940) a) Lange und Gewicht bei frühgeborenen Kindern im Schulalter b) Kopf umfang Thoraxmasse und Handkraft bei frühgeborenen Kindern im Schulalter c) Über Frühgeburtenstigmata und andere somatische Eigenheiten bei frühgeborenen Kindern im Schulalter Acta Paediat Uppsala, *28* suppl. 1 pp 39-49 50-73 and 74 100

Bronge A Hagberg B & Molin, L. (1960) Cataract in children. Aetiological aspects in a paediatric material. Nord.Med *64* 1033 1036

Brown C.A (1963) Postnatal cataracts in premature infants. Trans.ophthal.Soc UK *83* 493 504

Brown E V L & Kronfeld P C (1929) The refraction curve in the U.S.A with special reference to changes in the first two decades. XIII Concil Ophthal. pp 87-98 in Transactions, Amsterdam den Haag

Brown E V.L (1936) Apparent increase of hypermetropia up to the age of nine years. Amer.J Ophthal. *19* *1106*

Brown E V L (1938) Net average yearly changes in refraction of atropinized eyes from birth to beyond middle life Arch Ophthal. Chicago *19* 719 734

Brückner A (1954) Klinik der Refraktionsanomalien In Amsler Brückner Franceschetti, Goldmann & Streiff ed (*1954*) Lehrbuch der Augenheilkunde p 368 Karger Basel.

Brændstrup P (1943) Om den postoperative funktion ved cataract hos børn og unge Munksgaard København.

Bulpitt C.J & Baum J D (1969) Retinal photography in the newborn. Arch.Dis Childh *44* 499 503

Buschmann W (1963) Ein neues optisch akustisches Untersuchungsverfahren. Klin. Mbl. Augenheilk *142* 170-176

Buschmann, W (1964) Zur ultraschalldiagnostischen Messung der Achsenlange des Auges. Klin. Mbl.Augenheilk *144* 801-815

Buschmann, W (1966) Messungen der Achsenlange und anderer intraokularen Distanzen, in Einführung in die ophthalmologische Ultraschalldiagnostik, pp 72-84 Thieme Leipzig

Campbell, K (1951) Intensive oxygen therapy as a possible cause of retrolental fibroplasia. *Med J.Austr* *2* 48 50

Carpel E F & Kalina R.E (1973) Pupillary responses to mydriatic agents in premature infants. Amer.J Ophthal. *75* 988 991

Cass E.E (1937) *Divergent strabismus. Brit.J Ophthal.* *21* 538 559

Castrén J (1955) The significance of prematurity on the eye Acta Ophthal., Kbh. suppl. 44 Munksgaard

Catford G V & Oliver A (1973) Development of visual acuity Arch.Dis.Childh. *48* 47 50

Chace R R Merritt K.K & Bellows, M (1950) Ocular findings in the newborn infant. A preliminary report. Arch Ophthal. Chicago *44* 236 242

Churchill J.A (1965) The relationship between intelligence and birth weight in twins. Neurol. *15* 341 347

Coleman D.J Lizzi, F L. Franzen L.A & Abramson D.H (1973) A determination of the velocity of ultrasound in cataractous lenses SIDUO V Congress Gent (Plus personal communication by Abramson)

Crone R A & Velzeboer C.M.J (1956) Statistics on strabismus in the Amsterdam youth Arch Ophthal. Chicago *55* 455-47

Curtin B.J (1963) Pathogenesis of congenital myopia A study of 66 cases. Arch Ophthal Chicago *69* 166 173

Curtin B.J (1970) Myopia A review of its etiology pathogenesis and treatment Survey Oph thal. *15* 1 17

Dalsgaard I L & Nordentoft V (1970) Hæmorrhagia retinae hos nyfodte med særligt henblik på de vacuumforløste Nord.Med *83* 313

Dayton G O Jones M H Aiu P Rawson R.A Steele B & Rose M (1964) Developmental study of coordinated eye movements in the human infant Arch Ophthal. Chicago *71* 865 870

Delmarcelle Y & Luyckx Bacus J (1971) Évolution biométrique de la chambre antérieure chez l enfant Bull.Soc belg Ophtal *158* 451-465

Dixon W.J (ed) (1971) Biomedical computer programs UCLA Press Berkeley Los Angeles.

Doden, W & Protonotarios P.N (1960) Über Anamnese und Augenfunktionen gesunder Kinder Klin Mbl. Augenheilk *136* 459-476

Douglas A.A (1960) The eyes and vision in infantile cerebral palsy Trans ophthal.Soc.U.K *80* 311 325

Douglas A.A (1969) Children of reduced birth weight Clinics in Developmental Medicine *32* pp 82 86 Heinemann London

Downing A.H (1945) Ocular defects in sixty thousand American selectees. Arch. Ophthal. Chicago *33* 135 141

Drillien C.M (1964) The growth and development of the prematurely born infant Livingstone Edinburgh and London.

Duke-Elder S (1963) System of Ophthalmology vol. III Normal and abnormal development part I pp 304-313 Kimpton London

Duke-Elder S (1964) System of Ophthalmology vol. III Congenital deformities, part 2 p 333 Kimpton, London

Duke-Elder S (1969) The practice of refraction eighth ed p 206 Churchill London.

Duke-Elder S (1970) System of Ophthalmology vol. V Ophthalmic optics a ion pp 274 295 Kimpton London

Duke-Elder S (1970) System of Ophthalmology vol. V Ophthalmic optics and refraction. pp 218 219 Kimpton, London.

Dunlap E.A & Gaffney R.B (1963) Surgical management of intermittent exotropia. Amer.J Orthopt 13 311 325

Eames T.H (1946) Eye conditions among children of premature full-term and hypermature birth Amer.J Ophthal. 29 57-63

Ederer F (1973) Shall we count number of eyes or number of subjects. Editorial in Arch.Ophthal. Chicago 89 1 2

Ehlers N Matthiesen, M.E & Andersen H (1968) The prenatal growth of the human eye Acta Ophthal.Kbh 46 329 349

Eisler P (1930) Die Anatomie des menschlichen Auges pp 80-81 in Kurzes Handbuch der Ophthalmologie erster Band Springer Berlin.

Engbæk S (1970) Risk Children II Ugeskr Læg 132 57-67

Fantl, E.E & Perlstein M.A (1961) Ocular refractive characteristics in cerebral palsy Amer.J Dis Child 102 36-41

Faris B.M & Brockhurst R.J (1969) Retrolental fibroplasia in th cicatricial stage The complication of rhegmatogeneous retinal detachment Arch. Ophthal. Chicago 82 60-65

Faris B Tolentino F.I Freeman H.M Brockhurst R.J & Schepens C L. (1971) Retrolental fibroplasia in the cicatricial stage Fundus and vitreous findings. Arch.Ophthal. Chicago 85 661-668

Ffooks O O (1969) Neurophysiology and assessment of visual function in children. Brit.orthop J 26 10-14

Fled lius, H (1970) Ultrasound (A-mode) in a case of nasal posterior scleral ectasy Acta ophthal. Kbh. 48 502 507

Fledelius H (1971) Ultrasound oculometry and exophthalmometry in high myopia with reference to the occurrence of retinal detachment Acta Ophthal. Kbh. 49 707 714

Fledelius H & Alsbirk P.H (1973) Comparative TAU-oculometry SIDUO V Congress Gent

Fletcher M C & Brandon S (1955) Myopia of prematurity Amer.J Ophthal. 40 474-481

Fletcher M C & Silverman S.J (1966) Strabismus. Amer.J Ophthal. 61 86-94 and 255 267

Franceschetti, A Franceschetti A T & Hudson-Shaw S (1966) Erfassung von Augenstörungen durch Reihenuntersuchungen im Vorschulalter Klin.Mbl.Augenheilk. 149 657-66?

Franceschetti, A & Gernet H (1965) Über die optischen Grossen bei leichter und höher Myopie auf Grund echographischer B funde Graefes Arch Ophthal. 168 1 16

Franceschetti, A & Luyckx J (1966) Study of the emmetropization effect of the crystalline lens by ultrasonic echography Amer.J Ophthal. 61 1096 1100

Franceschetti, A T Linder A & Franceschetti A (1968) New results concerning the problem of axial lengths of the eye in anisometropia In Vanysek ed Diagnostica ultrasonica in ophthalmologia pp 235 238 Brno

Francois J (1959) Les cataractes congénitales. Masson Paris

Francois J & Goes F (1969) Comparative study of ultrasonic biometry of emmetropes and myopes with special reference to the heredity of myopia In Gitter Keeney Sarin & Meyer editors Ophthalmic ultrasound pp 165 180 Mosby St Louis

Francois J & Goes F (1970) Etude echographique de la myopie Bull.Soc belge Ophthal. *154* 415-430

Francois, J & Goes F (1973) Biométrie de la myopie Ophthalmologica *167* 49-65

Frandsen A.D (1958) Some results from a clinical statistical survey on strabismus among Copenhagen school children Acta Ophthal. Kbh *36* 488-498

Frandsen A D (1960) Occurrence of squint Acta Ophthal. Kbh suppl. 62

Franken S (1961) Metingen aan het levende menselijke oog met behulp van de echo van ultra sone trillingen Diss Utrecht

Franken S (1962) Measuring the length of the eye with the help of ultrasonic echo Ophthalmologica *143* 82 85

Fraser G R & Friedmann A I (1967) The causes of blindness in childhood A study of 776 children with severe visual handicaps. Hopkins Press Baltimore

Fridman F.E & Savitskaya N.F (1966) Ultrasound biometry in the study of the anatomo-optical elements of the eye in myopia Vestn Oftal *79* 30 33 ref from Zbl.ges Ophthal *97* 1966-67

Friis-Hansen B (1970) Oksygenbehandling af nyfødte In Medicinsk årbog XIII pp 167 182 Munksgaard København

Gardiner P (1954) The relation of myopia to growth Lancet I 476-479

Gedda E (1962) Prematurfödda skolbarn i Goteborg Svensk Lak Tidn *59* 100-108

Genn N.M & Silverman W.A (1964) The mental development of ex premature children with retrolental fibroplasia J.nerv.ment Dis *138* 79-86

Gernet H (1963) Zur Langenmessung des Auges am Lebenden Graefes Arch Ophthal. *166* 402-411

Gernet H (1964) Über Achsenlange und Brechkraft emmetroper lebenden Augen. Graefes Arch Ophthal *166* 424-431

Gernet H (1964) Achsenlange und Refraktion lebender Augen bei Neugeborenen Graefes Arch Ophthal. *166* 530 536

Gernet H (1967) Neueres zur Ultraschallbiometrie des Auges In Vanysek ed (1968) Diagnostica ultrasonica in ophthalmologia pp 217 234 Brno

Gernet H (1969) Datensammlung in der klinischen Oculometrie Docum ophthal. *27* 42-47

Gernet H (1969) Oculometriedaten bei Augengesunden. Ber dtsch.ophthal.Ges. *70* 597 599 publ. *1970*

Gernet H & Franceschetti, A *(1967) Ultrasound biometry of the eye (review) In* Ultrasonics in ophthalmology *pp 175 206* Karger Basel/New York.

Gernet H & Hollwich F (1968) Oculometrie des kindlichen Glaukoms. Ber dtsch.ophthal Ges. *69* 341 348 publ. 1969

Gernet H & Olbrich E *(1969) Excess of the human refraction curve and its cause. In Gitter* Keeney Sarin & Meyer ed Ophthalmic ultrasound pp 142 148 Mosby St Louis.

Gerstner R (1966) Langen oder Laufzeitmessung im Auge In Ultrasonics in ophthalmology pp 232 236 Karger Basel/New York (1967)

Gettes B C & Belmont O (1961) Tropicamide Comparative cycloplegic effects. Arch Ophthal. Chicago *66* 336 340

Gleiss J & Pau H (1952) Die Entwicklung der Refraktion von der Geburt Klin.Mbl.Augen heilk *121* 440-445

Glenting P *(1970) Etiology of congenital cerebral palsy* Diss. F.A D L København.

Goldschmidt E (1966) Myopia and height Acta Ophthal. Kbh *44* 751 761

Goldschmidt E (1968) On the etiology of myopia An epidemiological study Diss. Munksgaard Copenhagen

Goldschmidt E *(1969)* Refraction in the newborn. Acta Ophthal. *Kbh 47 570-578*

Graham M V & Gray O.P (1963) Refraction of premature babies eyes. Brit.med.J *1* 1452 1454

Grant *I C & Preston E.J (1960)* A *follow-up study of premature infants born in* Wake county 1948 51 N Carol.med.J *21* 446-449

Gregory I.D R (1957) Retinopathy of prematurity in children in whom the disease has not progressed *to complete* blindness and the subsequent investigation of cases of myopia. Brit.J *Ophthal 41* 321 327

Grieten *J & Weekers* R (1962) Etudes des dimensions de la chambre antérieure de l oeil humain Influence des amétropies. Ophthalmologica, *143* 56-66

Grignolo A & Rivara A (1968) Observations biométriques sur l oeil des enfants nés a terme et des prématurés au cours de la première annee Ann Oculist *201 817 826*

Grützner P Yazawa K *& Spivey B.E* (1970) Heredity and strabismus. Surv Ophthal. *14* 441 450

Guy L.P (1954) Postnatal cataracts *in premature* infants. Amer.J Ophthal. *38* 65-68

Gyll nsten L.J & Hellstrom B E (1952) Retinal fibroplasia animal experiments – the effect of intermittingly administered *oxygen* on *the postnatal development* of the eyes of full term mice Acta Paediat Uppsala *41* 577 582

Hansen E (1960) Cerebral palsy in Denmark Acta psychiat scand suppl 146

Harcourt R B *(1969) The objective assessment of visual function in young children* Brit orthop J *26* 1 9

Harley R D (1969) Pediatric ophthalmology In Nelson Vaughan & CcKay ed (1969) Text book of pediatrics ninth ed pp 1419 1436 Saunders Philadelphia

Harley J.D & Hertzberg R. *(1965)* Aetiology of cataracts in childhood Lancet 1 *1084 1086*

Harper P.A & Wiener G (1965) Sequelae of low birth weight Ann Rev Med *16* 405-420

Heimer C B Cutler R & Freedman A M (1964) Neurological sequelae of premature birth Amer.J.Dis Child *108* 122 133

Heinonen O *(1947) Das Geburtstrauma als Ursache des Schielens* Acta Ophthal. Kbh *25* 19 28

von Helmholz H (1896) Die Dioptrik des Auges In Handbuch der physiologischen Optik sec. edit pp 53 230 Voss, Hamburg/Leipzig

Hess J H & Lundeen E C *(1949)* The premature infant sec ed *Lippincott* Philadelphia

Hess J.H Mohr G.J & Bartelme P T (1934) The physical and mental growth of prematurely born children Univ.Press Chicago

Hiatt R L Costenbader F D & Albert D G (1965) Clinical evaluation of congenital myopia Arch Ophthal. Chicago *74* 31 35

Hirsch M.J (1952) The changes in refraction between the ages of 5 and 14 Theoretical and practical considerations *Amer.J Optom 29* 445-459

Hirsch M.J (1961) A longitudinal study of refractive state of children during the first six years of school Amer.J Optom *38* 564 571

Hirsch M.J (1963) Changes in astigmatism during the first eight years of school. Amer.J Optom *40* 127 132

Hirsch M.J (1964) The longitudinal study in refraction. Amer.J Optom *41* 137 141

Holm E (1926) Investigations of myopia in Danish secondary schools Acta Ophthal Kbh. *3* 121 130

Holm E (1949) *Retinopathia praematurorum* (retrolental fibrosis) Acta Ophthal. *Kbh 27* 623-631

Holst J C & Tjiland J (1962) Noen tall fra skoleoyelægekontoret i Oslo T norske Lægeforen. *19* 1291 1294

Hornblass A (1971) Persisting pupillary membrane and oxygen therapy in premature infants. Ann Ophthal. *3* 95 99

Hosaka A (1963) The ocular *findings* in the premature infants especially on the premature signs. Jap.J Ophthal. 7 77-81 ref from Zbl.ges Ophthal. *91* 1964

Huggert, A (1952) The appearance of the fundus oculi in premature infants, with special reference to the early stages of retrolental fibroplasia Acta Paediat Uppsala *41* 463-477

Hugonnier R & Clayette Hugonnier S (1969) Strabismus heterophoria ocular motor paralysis. Mosby St Louis.

Hyams, L. Safir A & Philpot J (1971) Studies in refraction II bias and accuracy of retinoscopy Arch.Ophthal. Chicago *85* 33-41

Illingworth R.S (1970) The development of the infant and young child 4th ed Livingstone Edinburgh

Ingram T.T.S & Kerr J D (1954) The association of retrolental fibroplasia with cerebral diplegia *Arch.Dis.Childh 29* 282 289

Jim, W & Brawand L. (1968) Etude échographique de la longeur axiale de l oeil avant et après l extraction du *cristallin* Ophthalmologica *156* 256 261

Jackson, E (1932) Norms of refraction. J.amer med.Ass. *98* 132 137

Jaeger W (1963) Augensymptome bei infantilen Zerebralparesen unter besonderer Berücksichtigung des Schielens. In Lindemann ed Die infantilen Zerebralparesen pp 120 142 Thieme Stuttgart

Jain I.S & Garg P.K (1970) Myopia in relation to prematurity J.All.Ind ophtahl.Soc *18* 89 98

Jansson, F (1963) Measurements of intraocular distances by ultrasound (A survey based on papers by Jansson et al. 1961-63) Acta Ophthal. Kbh. suppl. 74

Janus-Kukulska A & Lis S (1966) Developmental peculiarities of prematurely born children with birth-weight below 1250 g Develop.Med Child.Neurol. *8* 355 361

Johansen, E V (1950) Simple myopia in schoolboys in relation to body height and weight Acta Ophthal. Kbh *28* 355 361

Johnson D R & Swan K C (1966) Retrolental fibroplasia – a continuing problem Trans Pacif oto-ophthal. Soc *50* 129 133

Kalina R E (1969) Ophthalmic examination of children of low birth weight Amer.J Ophthal. *67* 134 136

Kamper J & Peitersen B (1973) Respiratory distress" syndrom hos nyfødte Ugeskr Læg *135* 2203 2206

Kantero R.L Frisk M & Holmstrom G (1965) Small prematures at 6 7 years of age Ann. Paediat.Fenn. *11* 169 174

Karlberg P (1973) Tilvaxt och utveckling In Nordisk lærebog i pædiatri 7th ed pp 8 20 Munksgaard København

Karpe G (1953) p *65* In Nordisk larobok i oftalmiatrik 5th ed Bonniers Stockholm

Kauffman M L (1958) Retinal hemorrhages in the newborn Amer.J Ophthal. *46* 658

Keeney A H (1951) Chronology of ophthalmic development Amer.Lect.Ser *99* Thomas Springfield/Illinois.

Khodadoust A.A Ziai, M & Biggs S L (1968) Optic disc in normal newborns Amer.J Ophthal. *66* 502 504

Kimura T Yamazaki, M Nakajima A Hayashi C & Nagata Y (1969) Analysis of errors in ultrasound biometry and phacometry In Gitter Keeney Sarin & Meyer ed Ophthalmic ultra sound pp 190-201 Mosby St Louis

King M.J (1950) Retrolental fibroplasia Arch Ophthal. Chicago *43* 694 711

Kinsey V.E (1956) Retrolental fibroplasia Cooperative study of retrolental fibroplasia and the use of oxygen Arch Ophthal. Chicago *56* 481 529

Kittel, V (1969) Beitrag zur Klinik der retrolentalen Fibroplasie Klin Mbl. Augenheilk. *155* 792 803

Knobloch H & Pasamanick B (1959) Syndrome of minimal cerebral damage in infancy J.amer med.Ass *170* 1384 1387

Knudtzon K (1941) On the frequency of eye diseases in Copenhagen school children. Acta Ophthal Kbh *19* 174 179

Knudtzon K (1942) Social medical experiences from the school for children with defective vision in Copenhagen Acta Ophthal *20* 194 204

Kosoff G & Robinson D.E (1967) Basic physics of diagnostic ultrasound In Goldberg & Sarin ed Ultrasonics in ophthalmology Saunders Philadelphia and London

Krause A C (1955) Effect of retrolental fibroplasia in children. Arch. Ophthal. Chicago *53* 522 529

Kronfeld P C & Devney C (1930) The frequency of astigmatism Arch.Ophthal. Chicago *4* 873-884

Lang R F (1920) The position of the axis in astigmatism and the amount of the astigmatic error From an analysis of four thousand prescriptions Brit.J Ophthal. *4* 126 128

Larsen J.S (1971) The sagittal growth of the eye I IV Acta Ophthal. Kbh *49* [illegible] 427-440 441-453 873-886

Leary G.A Sorsby A Richards, M.J & Chaston J (1963) Ultrasonographic of the components of ocular refraction in life Vision Res. *3* 487-498

Lewkonia I (1969) Objective assessment of visual acuity by induction of optokinetic mus. Brit.J Ophthal. *53* 641-644

Liebman S D (1955) Postnatal development of lamellar cataracts in premature infants Arch. Ophthal. Chicago *54* 257 258

Liesmaa M (1972) Congenital cataract and ectopia lentis. An analysis of 152 patients treated in 1943 1967 Acta Ophthal Kbh Suppl. 112

Lind J (1969) Det nyfödda barnets adaptation Nord.Med *82* 1561 1570

Lindstedt E (1969) Causes of blindness in Sweeden Acta Ophthal Kbh suppl. 104

Lippmann O (1969) Vision of young children Arch Ophthal. Chicago *81* 763 765

Litvinova M.P Volokitenko A.E & Pikalova L.D (1964) Refraction and binocular vision in children under school age Oftal.Zh *2* 87 91 ref from Ophthalmic Lit *18* (1964)

Lomickova H (1964) Notes on myopia in premature infants Cs Oftal *20* 195 201 ref from Ophthalmic. Lit *18* (1964)

Lowe R F (1968) Time-amplitude ultrasonography for ocular biometry Amer.J Ophthal. *66* 913 918

Lubchenco L O (1968) Outcome for low birth weight infants In Barnett s Pediatrics, 14th ed pp 100-108 Appleton-Century-Crofts New York.

Luyckx J (1966) Mesure des composantes optiques de l oeil du nouveau né par echographie ultrasonique Arch Ophtal Paris *26* 159 170

Luyckx Bacus J & Weekers J F (1966) Étude biométrique de l oeil humain par ultrasonographie Bull.Soc belge Ophtal. *143* 552 567

Luyckx J & Delmarcelle Y (1971) Biométrie du globe oculaire en fonction de l age et de la refraction chez l enfant SIDUO IV congress Paris In Massin & Poujol ed (1973) Diagnostica ultrasonica in ophtalmologia pp 269 275 Paris

Lyle T K & Bridgeman G.J O (1959) In Worth and Chavasse s squint Bailliere Tindall and Cox London

Marquardt R & Weber-Causé A (1968) Untersuchungen von Kindergartenkindern mit dem Rodenstock-Sehtestgerat RS Klin.Mbl.Augenheilk *152* 421-425

Marstrander J (1965) A prospective study of mental and motoric development in premature children with birth weights less than 2000 gm Acta Paediat scan suppl 159 71 73

Mathew M & Sawney B.K (1970) Refraction in the newborn Orient Arch Opthal *8* 65 68

Matthiessen P C Trolle D & Zachau-Christiansen B (1967) Infant and perinatal mortality in Denmark Publ Health Serv Publ no 1000 Washington D C

Mauthner L (1876) Vorlesungen über die optischen Fehler des Auges Baumüller Wien

McCormick A Q (1968) Transient cataracts in premature infants Canad J Ophthal *6* 178 182

McDonald A (1962) Neurological and ophthalmic disorders in children of very low birth weight Brit med J 1 895 900

McDonald A (1967) Children of very low birth weight M E I U research monograph no I Heinemann ltd London

McKay R.J (1960) The high risk infant In Nelson s textbook of pediatrics 9th ed pp 360 371 Saunders Philadelphia

McKeown T & Record R G (1960) vide Villumsen (1970) Environmental factors in congenital malformations p 20

McLaren D.S (1961) The refraction of Indian school children Brit J Ophthal *45* 604-613

McLaughlan G.P (1963) The growth and development of premature babies Med Offr *109* 245 250

McNeil N L (1955) Patterns of visual defects in children Brit J Ophthal *39* 688 701

McNeil N L (1956) Some ocular manifestations of prematurity Brit J Ophthal *40* 24 29

Mellick A (1949) Convergence An investigation into the normal standards and age groups Brit J Ophthal *33* 755 763

Mendelson M Weiss W Deutschberger J Shakhashiri, Z.A & Jackson E (1966) The assessment of mental and motor development at eight months of age In compilation of papers presented at the meeting of the collaborative study on cerebral palsy mental retardation and other neurological disorders of infancy and childhood Part II pp 64 79 U.S Dept Helth Educ & Welf Publ Health Service Washington D C

Merin S & Crawford J.S (1971) The etiology of congenital cataracts A survey of 386 cases Cand J Ophthal 6 178 182

Milder B (1961) Tropicamide as a cycloplegic agent Arch Ophthal. Chicago *66* 70 72

Miranda N.M (1972) Residual accomodation Arch Ophthal Chicago *87* 515 517

Molnár L (1961) Refraktionsuntersuchungen an Frühgeborenen und Sauglingen Graefes Arch Ophthal *163* 518 526

Moller D.E (1970) Über die Haufigkeit von Augenveranderungen bei Frühgeburten Klin.Mbl Augenheilk *156* 654-661

Mundt G.H & Hughes W F (1956) Ultrasonics in ocular diagnosis Amer J Ophthal. *41* 488 498

Murphy A.M Reid R R Pollard I Gillespie A.M Dorman D C Menser M.A Harley J D & Hertzberg R (1976) Rubella cataracts Amer J Ophthal. *64* 1109 1119

Mushin A (1971) Ocular changes in premature babies receiving controlled oxygen therapy in the neonatal period Proc roy Soc Med *64* 779 780

Nakajima A & Kimura T (1967) Ultrasonography and phakometry in study of refra elements of the eye In Ultrasonics in ophthalmology pp 226 231 Karger Basel/New Y

Nauheim J.S (1960) Heterotopia of the macula Arch Ophthal. Chicago *63* 144 156

Nawratzki I & Oliver M (1970) The screening of pre-school children for the early detection of certain ocular defects. At the XXI Concil.Ophthal. Mexico Acta pars I pp 978 982 Amsterdam 1971

Neuman, J (1963) Ein Beitrag zur retrolentalen Fibroplasie Klin.Mbl.Augenheilk *142* 802 808

Neumann, E Eibschitz N., Hyams, S & Friedman Z (1971) Ophthalmic screening in child welfare clinics in Israel with special reference to strabismus and amblyopia J ped Ophthal. *8* 257 260

von Noorden G K & Khodadoust A (1973) Retinal hemorrhage in newborns and organic amblyopia Arch.Ophthal. Chicago *89* 91 93

Nordlow W (1949) To the accuracy of the objective and subjective method by determining the refraction of the eye Acta Ophthal. Kbh *27* 349 378

Nordlow W (1964) Squint – the frequency of onset at different ages and the incidence of some associated defects in a Swedish population. Acta Ophthal. Kbh. *42* 1015 1037

Nordmann J (1966) Early postnatal cataracts. Amer.J Ophthal. *61* 1256 1263

Nordmann J Klehti, J & Gerhard J.P (1970) Observations of congenital and early postnatal cataracts Ann Oculist *203* 600

Norn, M.S Rindziunski, E & Skydsgaard H (1969) Ophthalmic and orthoptic examinations of dyslectics. Acta Ophthal. *47* 147 160

Norris M Spaulding P.J & Brodie F.H (1957) Blindness in children Univ Chicago Press. Cited from a book review by D Shoch (1957) Amer.J Ophtal. *44* 555

Nover A & Grote W (1965) Über die Bestimmung der Achsenlange des menschlichen Auges mit Ultraschall am Lebenden Graefes Arch.Ophthal. *168* 405-418

Nørregaard S (1953) Aarsagerne til for tidlig fødsel. Diss. Frost Hansen København

Oksala A (1964) The clinical value of time-amplitude ultrasonography Amer.J Ophthal. *57* 453-460

Oksala A (1967) Basic problems in A-mode ultrasonography In Goldberg & Sarin ed Ultra sonics in ophthalmology pp 76-86 Saunders Philadelphia/London

Oppel O (1964) Über die Entwicklung der Sehschärfe bei Kindern im Vorschulalter Klin.Mbl. Augenheilk. *145* 358 371

Ossoinig K (1968) Additional experiences with phantoms as aids in the ultrasonic diagnosis of intraocular tumors. In Vanysek ed. Diagnostica ultrasonica in ophthalmologia Brno

Owens, W C (1955) Symposium on retrolental fibroplasia Clinical course Amer.J Ophthal. *40* 159 162

Owens W C & Owens, E U (1949) Retrolental fibroplasia in premature infants. Amer.J Ophthal. *32* 1 18

Schiøttz-Christensen E (1972) Genetic factors in febrile convulsions An investigation of 64 same-sexed twin pairs Acta neurol scand *48* 538 546

Schiøttz-Christensen E (1973) Neurological findings in twins discordant for febrile convulsions. Acta neurol.scand *49* 368 378

Schlossman A & Borochoff S.A (1955) Correlation between physiologic and clinical aspects of exotropia Amer.J Ophthal *40* 53-64

Schnabel J & Herrnheiser J (1895) Über Staphyloma posticum Conus und Myopie Z.Heilk *16* 1-48

Schoberlein W (1938) Zur Frage der Entwicklung der Unreifgeborenen Mschr Kinderheilk *76* 80 106

Scobee R G (1951) Esotropia Incidence etiology and results of therapy Amer.J Ophthal. *34* 817-833

Seedorff T (1968) Retrolental fibroplasia Acta Ophthal Kbh *46* 500 506

Seissiger J (1929) Augenbefunde bei Neugeborenen Archiv Augenheilk *100 101* 302 313

Sezen F (1970) Retinal haemorrhages in newborn infants Brit.J Ophthal. *55* 248 253

Shoch D (1957) vide Norris et al.

Siegel, S (1956) Nonparametric statistics for the behavioral sciences International student ed Kogakusha Tokyo

Silverman W.A (1969) Prematurity and retrolental fibroplasia Sight Sav Rev *39* 42-46

Skydsgaard H B (1973) Discussion to Seedorff H H at Nordic Ophthalmic Congress Turku (Not printed in congress report)

Skydsgaard H.B (1974) Personal communication

Slataper F.J (1950) Age norms of refraction and vision Arch Ophthal. Chicago *43* 446 481

Smith V H (1963) A survey of strabismus in cerebral palsy Little Club Clinics in Developm Med *9* 22 36

Smith V.H (1969) A screening service for the early detection of visual handicap Clin Developm Med *32* 71 74 Heinemann, London

Snedecor G W & Cochran W G (1967) Statistical methods 6th ed Iowa State Univ.Press, U.S.A

Sobański J Domzal B Sulta T & Zelawska H (1962) Über die physiologische Entwicklung des primitiven Sehens der Fixation und des binokularen Sehens. Ophthalmologica *143* 20-24

Sorsby A (1934) The pre-myopic state its bearing on the incidence of myopia Trans.ophthal. Soc U.K. *54* 459-465

Sorsby A (1964) The nature of spherical refractive errors. In Modern ophthalmology vol. 3 pp 1 20 Butterworth London

Sorsby A. (1972) The nature of spherical refractive errors. In Modern ophthalmology sec.ed vol. 3 pp 9 29 Butterwoths, London

Sorsby A Sheridan M Moores N & Haythorne J (1955) Hyoscine cycloplegia in children. Lancet u, 214-215

Sorsby A. Benjamin B Davey J B & Tanner J.M (1957) Emmetropia and its aberrations. A study in the correlation of the optical components of the eye Med Res Counc.Spec Rep.Ser no 293 London.

Sorsby A Benjamin B & Sheridan M (1961) Refraction and its components during the growth of the eye from the age of three Med Res Counc.Spec Rep.Ser no 301 London

Sorsby A & Leary G.A (1970) A longitudinal study of refraction and its components during growth Med.Res.Counc.Spec Rep.Ser no 309 London

Sourasky A (1928) Race sex and environment in the development of myopia Brit.J Ophthal. *12* 197 212

Steiger A (1895) Beitrag zur Physiologie und Pathologie der Hornhautrefraktion. Cited from Duke-Elder (1970) System of Ophthalmology vol. V p 275

Steiger A (1913) Die Entstehung der spharischen Refraktionen des menschlichen Auges. Berlin

Stenstrom S (1946) Untersuchungen über die Variation und Kovariation der optischen Elemente des menschlichen Auges Acta Ophthal. Kbh. suppl 24

Stern S.D & Arenberg I.K (1969) Heterotopia of the macula associated with retinal detachment A case report J ped Ophthal. *6* 198 202

Streiff E B (1969) L examen des fonctions oculaires jusqu a l age de 6 ans. Ophthalmologica *158* 488 503

Stromberg E (1936) Über Refraktion und Achsenlänge des menschlichen Auges.Acta Ophthal. Kbh *14* 281 293

Stuart H C & Stevenson S.S (1959) Tables of norms for use as reference standards in the evaluation of body measurements (Data collected 1930-1946 on Iowa city children of north west European ancestry by H V Meredith) In Nelson s textbook of pediatrics 7th ed pp 47 61 Saunders Philadelphia (The tables are also printed in Documenta Geigy (1962) 6th ed pp 613-622)

Stocklin, P (1957) Normvarianten der Morphologie der kindlichen Linse Graefes Arch.Ophthal. *158* 346 359

Sundal, A (1962) Norms for height and weight for healthy Norwegian children from birth to 15 years of age In Nordisk lærebog i pædiatri 5th ed., pp 17 26 Munksgaard København.

Svedbergh B & Lindstedt E (1973) Retrolental fibroplasia in Sweeden. General survey and selected study on patients born in 1960 1966 Acta Paediat scand 62 458-464

Szirmak E & Pajor R (1971) Fundusuntersuchungen bei Frühgeburten und reifen Neugeborenen Med.Mschr *25* 216 219

Sorensen S.K (1944) L astigmatisme du cristallin determiné comme la différence entre l astig matisme cornéen et l astigmatisme total illustré par l examen de ses variations d apres l age Acta Ophthal. Kbh *22* 341 351

Tait E C (1966) Intraocular astigmatism in children J ped Ophthal. *3* 49 52

Tait E.F (1951) Accomodative convergence Amer.J Ophthal *34* 1093 1107

Takkunen R L. Frisk M & Holmström G (1965) Follow-up examination of 110 small prematures at the age of 6 7 years Acta Paediat scand Suppl. 159 70 71

Tassman W & Annesley W (1966) Retinal detachment in the retinopathy of prematurity Arch Ophthal. Chicago *75* 608-614

Terry T L (1942) Extreme prematurity and fibroplastic overgrowth of persistent vascular sheath behind each crystalline lens. Amer.J Ophthal. *25* 203 204

Therkelsen A.J (1968) Medicinsk statistik Akademisk Boghandel Århus.

Thomson E (1924) Some considerations regarding the aetiology the incidence and the course of concomitant convergent strabismus which have bearing upon its treatment Trans ophthal. Soc U.K. *44* 238 270

Tizard J.P.M (1971) Modern management of oxygen therapy in the newborn Proc.roy Soc.Med *64* 771 773

Tron E (1929) Variationsstatistische Untersuchungen über Refraktion. Graefes Arch.Ophthal. *122* 1 33

Tron E (1934) Über die optischen Grundlagen der Ametropie Graefes Arch Ophthal *132* 182 223

Tscherning M (1886) Om afhængigheden mellem corneas krumning legemshøjden og hovedets omfang Hospitalstidende *4* 1129 1140

Tscherning M (1898) Optique physiologique Carré & Nauel. Paris.

Tornquist R (1953) Shallow anterior chamber in acute glaucoma. Acta Ophthal. Kbh. suppl. 39

Villumsen, Aa L (1970) Environmental factors in congenital malformations. Diss. F.A.D L. København

Vogt A (1919) Beobachtungen an der Spaltenlampe über eine normalerweise den Hyaloidrest der Hinterkapsel umziehende weisse Bogenlinie Archiv f Ophthalmologie *100* 349 356

Wagner G (1957) Augenbefunde bei Frühgeburten. Klin.Mbl.Augenheilk. *131* 326 334

Watzke R C (1961) The ophthalmoscopic sign "white with pressure" Arch Ophthal. Chicago *66* 813-823

Weekers, R., Watillon M & Thomas-Decorts, G (1961) La myopie des prématurés, facteur de dissemblance dans la refraction des jumeaux monozygotes. Arch.Ophtal. Paris, *21* 217 226

Weiss, L. (1897) Über das Wachstum des menschlichen Auges und über die Veranderung der Muskelinsertionen am wachsenden Auge Arb.Anat.Inst.Wiesbanden *8* 191 (cited from Sorsby et al. (1961))

Weymouth F W (1916) An experimental comparison of three common methods of measuring heterophoria. – Reprinted (1963) in Amer.J Optom *40* 497 504

Weymouth F W & Hirsch M.J (1950) Relative growth of the eye Amer.J Optom *27* 317 328

Wibaut F (1926) Über die Emmetropisation und den Ursprung der sphärischen Refraktions-anomalien. Graefes Arch Ophthal. *116* 596-612

Wibaut F (1932) Biologisch-statistische Refraktionsuntersuchungen. Bergmann München.

Wiener G (1968) Scholastic achievement at age 12 13 of prematurely born infants J Soc Educ *2* 237 250

Williams, C.E (1958) Retrolental fibroplasia in association with mental defect Brit.J Ophthal. *42* 549 557

Wolff E (1948) The anatomy of the eye and orbit Third ed pp 375 379 Lewis & Co London.

World Health Organization (WHO 1948 1950) discussed by Drillien 1964 McKay 1969 and Raiha 1973

Wyatt H T & Boyd T.A.S (1973) Strabismus and strabismic amblyopia in Northern Canada Canad.J Ophthal. *8* 244-251

Yamamoto A Namiki, R Baba M & Kate M (1961) A study on the measurement of ocular axial length by ultrasonic echography Jap.J Ophthal. *5* 134 139

Ylppo A (1919) Zur Physiologie Klinik und zum Schicksaal der Frühgeborenen Z Kinderheilk *24* 1 110

Ylppo A (1919) Das Wachstum der Frühgeborenen von der Geburt bis zum Schulalter Z Kinderheilk. *24* 111 178

Zacharias, L. Chisholm J.F & Chapman R B (1962) Visual and ocular damag in retrolental fibroplasia Amer.J Ophthal. *53* 337 345

Zachau-Christiansen B (1972) The influence of prenatal and perinatal factors on development during the first year of life P.A Andersens Forlag Helsingor

Ziegler A (1960) Cataracte et anoxie chez le prématuré Ann.paediat Basel *194* 76 89

Zilberman R.S (1963) The state of vision and refraction in town and village schoolchildren Oftal Z *18* 47-48 ref from Zbl ges Ophthal. 1963

Østerberg J & Kjærgaard C (1964) En synsundersøgelse af skolebørn Ugeskr Læg *126* 6?? 664

SUBJECT INDEX

Accommodation 44
Aetiologic considerations 72 111 156 193
Age 24 28 101
Anisometropia 59 93 152
Anterior chamber depth 45 80 82 85
Asphyxia 73 156 194
Astigmatism 53 60 69 71
Axial length of the eye 79
  growth curve 75 76
  measurement 32 35-45

Basic material 19
Binocular deviants 146 148
Binocular function 127
Binocular function tests 31 32 136 137
Binocular visual acuity 31 117 187 193
Birth weight 13 22 26
  and per entile height 101
  and refraction 59 62
Blindness 11 15 117 122
Brain damage 15 16 153 195

Cataract
  congenital 117 171 183
  false posterior 176
  of prematurity 11 172 178
Central nervous system damage 130 153 195
Cerebral haemorrhage 17 130
Cerebral palsy 11 131 197
Chavasse stereopsis 136 146
Cloudy ocular media 21 159
Colour sense defects 32 183
Comparability 27 193
Concomitant squint 148
Condition neonatally 73 153
Congenital
  cataract (vide cataract)
  malformations 181
  myopia 50 63
Contact glass (oculometry) 36 42

Corneal
  astigmatism 53 71
  curvature radius (vide keratometry)
  pathology 183
  refractive power 83 86 95
  transverse diameter 32 106 109
Correlation right left eye 57 59 79
Covariation of refractive components 78 85 89 94 106
Cross-sectional studies, 47 76
Cycloplegia 44 52 77 175

Determinative oxygen, 15
Dizygotic twins, 186
Dragged disc 161

Early myopia 63
Educational deviants 195
Emmetropia eye size in, 77 91 96
Esophoria 135
Esotropia 135 151
Eso-Exo ratio 132 140
Exophoria 135
Exophthalmometry 32 105 109
Exotropia 135

Functional immaturity 13 14
Fusion 136 142

Gestational age 25 190
Glaucoma 167 182
Growth patterns 99 109

Height
  of child 32 101 108 187
  of mother 102
  and refraction 110
Hereditary factors, 28 67 156 177 181

Heterophoria 135 139 151
low (physiological) 135 139
high (unphysiological) 135 139
Heterotropia 135 139
High myopia 62 97

Illegitimate birth 21
Incomitant squint 148
Incubator (oxygen treatment) 15 169
Individuals or eyes 33 57
Interferometer (oculometry) 37 39
Interpupillary distance 32 105 187
Iris colour 183

Keratometry 32 53 83 187

Lens
opacities, 171 176
refractive power 96
thickness, 82
Liberal oxygen 15
Longitudinal series 47 76
Low birth weight 13 14

Macroscopic cataract 176 177
Macular changes 162 166
Maddox tests 136
Major retinal damage 162 166
Matched pairs 186
Mature control group 23
"Maturity difference" 81 85 94 101 105 106 109 199
Microtropia 135
Minimal cerebral damage 11 16
Minor retinal damage 162 166 169
Mittendorf's dot 175
Monocular visual acuity 31 120 190
Monozygotic twins, 186
Motor imbalance (binocular)
horizontal (vide eso- and exo-)
vertical 140
Multiple birth 26 185 194
Multiple stepwise regression, 89
Myopia
of prematurity 11 49 199
at pre-school age 50 63 64 92 96 119 122 152 199
in retrolental fibroplasia 49 51

Near point of accommodation, 136 141
Near point of convergence 136 141
Neonatal care 14
Neonatal icterus, 73 153
Neonatal mortality 11 20
Nystagmus 183

Obstetric-paediatric data 19 193
Ocular motility 31
Ocular protrusion (vide exophthalmometry)
Ophthalmic examination scheme 31
Ophthalmic handicap 200
Ophthalmoscopy 159
Optic cup 167
Optic (nerve) atrophy 167
Optical calculations 94
Optical pachymetry 35
Optimum birth weight 13 24 27
Optokinetic nystagmus 113
Orthophoria 135 138
Oxygen treatment 15 153 169 170

Participation rate 22 24
Percentile height 101
Perinatal damage syndrome 174
Persistent pupillary membrane 175 176
Phakometry 35 76
Premature group (present series) 22
Prematurity 13
Prematurity trauma 12 74 111 156 200
Prematurity in squint series 130
Pre-school myopia (vide myopia)
Proteinuria (maternal) 194
Ptosis 181

Racial factors 16 29
Refraction
in childhood 47
components 75 79 187
curves 70
and height 108 110
in premature series 49 51
and squint 151
values (present results) 53 187
Remnants of hyaloid system and vascular sheaths of the lens, 175 176
Representativeness 26
Residual astigmatism 71
Respiratory distress syndrome 15
Restrictive oxygen, 15
Retinal
correspondence 146 149
haemorrhage 17 160
pigmentary changes 162 166
tortuosity 161 167 169
Retinoscopy 31 52
Retrolental fibroplasia (RLF) 11 15 117 160 161 168 174 177

Risk groups 124 170 200

Sex difference 78 81 82 84 94 101 105
Simultaneous perception 136
Single-birth children 187
Skewness towards myopia 54
Small-angle heterotropia 149
Smoking habits during pregnancy 73 124
153 194
Social factors 16 21 29 48 110 124
153 193
Somatic parameters 99 105
Sources of error in oculometry 41
Spherical equivalent 53
Squint
due to brain lesions 17 130 195
latent (vide heterophoria)
manifest (vide heterotropia)
prevalence of 128
(vide also binocular function)
Statistical methods, 32
Stereopsis 136 145
Strabismus (vide squint)
convergent (vide eso-)
divergent (vide exo-)
Sturge-Weber haemangioma 167 182
Synoptophore 32 136

Tapeto-retinal degeneration 168
Thin fundus (albinoid) 162 166
Time-amplitude ultrasonography (TAU) 36
159 183
Titmus test 32 136
Tobacco (vide smoking habits)
Tortuosity (vide retinal t)
Toxaemia (vide proteinuria)

Ultrasound
calibration 37 40
oculometry 34 35 76 79
transducers 36 41
(vide also Time-amplitude U)
Uncoordinated gaze 21
University of Copenhagen Project 1959-61
19

Visual
acuity (vide binoc and monoc. vis.ac)
acuity testing at school, 23 115
Visual defect (or handicap) 115 122 124
200
Visual field defects, 113
Vitreous length 82
Vitreous opacities 183

WHO 13
Wirt stereotest (vide Titmus)
Worth four dot test 136 142

X-ray oculometry 35

APPENDIX

The appendix comprises the 41 abbreviated case histories referred to in the chapters above The cases are listed according to their sequence in text and tables The original record numbers (from the *basic* material cf chapter 2) are given in brackets with A or B added *in cases of multiple* birth

Abbreviations

AL	Axial length
BW	Birth weight
f and m	Female and male
GA	Gestational age
OPHTH	Ophthalmoscopy
OX	Oxygen treatment
PEX	Present examination
RD	Retinal detachment
RE and LE	Right eye and left eye
RLF	Retrolental fibroplasia
TAU	Time amplitude ultrasonography
VRE and VLE	Visual acuity of RE and of LE

No 1 m (31993 B) RLF stage V phthisis corneal dystrophy cataract nystagmus, ptosis.
BW 900 g GA 28 weeks OX 40% in incubator for 12 h by funnel 15 days.
(Twin A a girl, BW 1100 g normal eye status at PEX)
RLF developed during the first three months bilateral surgery for glaucoma Educated at Refsnæsskolen (The Danish Boarding School for the Blind and Weak-sighted) Behavioural difficulties organic psycho-syndrome"
PEX Blind (no light perception) deep-set phthisical eyes with corneal opacification ant and post synechias, cataract coarse nystagmus decreased eye motility ptosis
TAU AL around 12 mm Sound reflecting structures throughout the vitreous

No 2 f (51723) RLF stage III IV eso and hypertropia early myopia nystagmus
BW 1500 g GA not stated OX 40% in incubator for 12 h by funnel for 8 days
9 days old opaque media but no RD At 5 months bilateral falciform RD from disc and temporally 5 years old surgery for esotropia Attending a class for weak-sighted

PEX VRE 3/60 −4 0 VLE finger counting 20 cm (−3 0)
Deep-set eyes coarse nystagmus eso and hypertertropia of LE strands of pup mem brane OPHTH bilateral falciform RD thin stretched retinal vessels pigmentary changes.
TAU AL 23 9 mm RE 21 4 mm LE anterior chamber depths 3 9 and 3 3 mm

No 3 m (50772) RLF stage II III esotropia nystagmus early myopia
BW 1250 g GA 29 weeks. OX 40% in incubator for 3 h by funnel 8 days
4 weeks old opaque media 1 year old myopia nystagmus pallor of malformed discs falciform RD of LE Surgery for esotropia Spastic diplegia
PEX VRE 6/18 −8 0 −2 0 X 180 VLE 1/36 −9 0
Latent nystagmus lateral gaze nystagmus eso and hypertropia deviation increasing on gaze upwards and left OPHTH RLF with dragged discs thin stretched ret vessels pig mentary changes, falciform RD of LE

No 4 f (50278) RLF stage I III cataract lens coloboma esotropia early myopia anisome tropia
BW 1300 g GA 29 weeks. OX 40% in incubator for 5 h by funnel 4 days and again for 6 days after a five-day interval.
At 4 years glasses for myopia
PEX VRE 3/60 −4 0 (heterotopic fixation head tilt) VLE 6/18 −1 0 −1.0 X 100
Esotropia of RE localized cloudy cataracts bilaterally lens coloboma of RE OPHTH opaque media a retinal fold passing the macula of RE stretched vessels of LE
TAU AL 24 7 mm RE 23 0 mm LE

No 5 m (51766) RLF I III exotropia early myopia anisometropia nystagmus
BW 1350 g GA 28 weeks OX by funnel for 24 h
Amblyopia and myopia diagnosed at the age of 5 Spastic diplegia
PEX VRE 1/60 −14 0 VLE 6/12 −2 5 −0 75 X 90
Pseudo-esotropia of RE due to heterotopia of macula decreased adduction of RE nystagmus (coarse of RE latent of LE) iris atrophy and localized cataract of RE OPHTH dragged disc stretched vessels pale fundus gliosis of macular region (fold?) in RE LE normal
TAU AL 25 2 mm RE 24.5 mm LE

No 6 m (12051) Early myopia anisometropia esotropia.
BW 1350 g GA 32 weeks. OX 40% in incubator for 7 h by funnel 24 h Esotropia since birth early myopia
PEX VRE 6/6 −0,5 VLE 6/12 −4 0
OPHTH temporal conus of LE
TAU AL 22 7 mm RE 24.5 mm LE

No 7 m (22688) Pigmentary changes in LE fundus.
BW 1950 g GA 36 weeks. OX 35% in incubator for 10 h
PEX VRE and VLE 6/6+0 75
OPHTH choroido-retinal pigment scar in temporal periphery of LE slight tortuosity

No 8 m (30173) Unilateral high myopia anisometropia
BW 1470 g GA 30 weeks. OX by funnel for 12 days.
PEX VRE light sense with projection −14 0 VLE 6/4.5 +1 5
No heterotropia in cover tests. OPHTH pale fundus of RE
TAU AL 26 2 mm RE 22 1 mm LE

No 9 f (30569 A) Pigmentary changes of LE myopia.
BW 1650 g GA 31 weeks. OX by funnel for 24 h

(Twin B f BW 1550 g normal eye status at PEX)

PEX VRE >6/6 emm VRE <6/6 -0 5
OPHTH pigmentary crescent at the *nasal* border of the left optic disc no traction of vessels

TAU AL 23 9 mm RE 24 0 mm LE

No 10 m (31637) Early myopia anisometropia vitreous opacities
BW 1200 g GA 28 weeks. OX 40% in incubator for 11 h by funnel 4 days.
Mental deficiency hearing loss Surgery for esotropia Early myopia

PEX VRE 6/36 -4 0 VLE 6/9 -1 0
Slight esotropia suppression of RE by binoc sensory tests.
OPHTH opacities of vitreous RE fundi pale foveal reflexes not present

TAU AL 24 2 mm RE 23 6 mm LE

No 11 m (41732) Early myopia anisometropia
BW 1400 g GA 33 weeks. OX 35% in incubator for 24 h
Early myopia

PEX VRE <6/6 -6 75 -0 5 X 180 VLE 6/6 -3 0 -0.5 X 180
OPHTH pale fundus espec of RE inverse vessel emergence

TAU AL 26 9 mm RE 23.5 mm LE

No 12 f (42293) Unilateral, early myopia anisometropia lid coloboma
BW 1800 g GA 36 weeks OX 35% in incubator for 80 h
Esotropia in infancy

PEX VRE >6/9 +2.5 VLE >6/12 -6 5
Now exo- and hypertropia 1x3 mm notch of right upper eye lid
OPHTH pale fundus and disc of LE

TAU AL 23 8 mm RE 27 3 mm LE

No 13 m (50195 B) Unilateral high myopia anisometropia esotropia
BW 1750 g GA 31 weeks. OX 40% in incubator for 3 h
(Twin A BW 1550 g normal eye status at PEX)
6 years old surgery for esotropia of LE

PEX VRE 6/6 +1.5 VLE 1/36 -17 0
OPHYH very pale fundus of LE

TAU AL 22 3 mm RE 29 1 mm LE

No 14 f (50929) Early myopia esotropia.
BW 1900 g GA 32 weeks. OX 40% in incubator for 30 minutes by funnel 24 h.
Congenital esotropia (alternating) epilepsy or hypoglycaemic attacks

PEX VRE <6/9 -3 0 -0 5 X 90 VLE <6/9 -3 25
OPHTH slight pallor of fundi.

No 15 f (51525) Esotropia mixed astigmatism
BW 1200 g GA 30 weeks. OX 40% in incubator for 2 h
3 years old glasses for astigmatism

PEX VRE 6/12 +1.5 -2 0 X 30 VLE 6/36 +1.5 -2 0 X 170
Latent nystagmus binocular corrected vision >6/12 esotropia of LE epicanthus.
OPHTH pigm changes in temp periphery of LE medium tortuosity

TAU AL 21 9 mm LE

No 16 f (51573) Hypermetropic astigmatism tortuosity retinal pigmentary changes.
BW 1200 g GA 30 weeks. OX 40% in incubator for 2 h by funnel 12 days. Neonatal jaundice exchange transfusions x 3

PEX VRE >6/9 +3 0 +0 75 X 160 VLE <6/6 +3 0 +0 75 X 20
OPHTH slight pigmentary changes in both fundi extreme tortuosity

No 17 f (51577) Early myopia tortuosity choroido retinal scars
BW 1600 g GA 35 weeks. OX 40% in incubator for 8 h by funnel 11 days.
Neurosis organic psycho-syndrome
PEX VRE 6/12 –4 5 VLE 6/6 –6 0
OPHTH pale fundi discs obliquely elliptical extreme tortuosity foveal reflexes absent rounded choroido-retinal scarifications one in each eye
TAU AL 24.5 mm RE 25 2 mm LE

No 18 m (51699) Myopia anisometropia.
BW 1300 g GA 31 weeks. OX 40% in incubator for 3 h intermitt by funnel for 8 days
Congenital esotropia since the age of three occlusion therapy
PEX VRE <6/6 –1 0 –1 0 X 20 VLE 6/24 –6 0 –1 0 X 180
Eso- and hypertropia sensory depression of LE OPHTH pale fundus of LE and foveal reflex almost absent.
TAU AL 23 2 mm RE 24 0 mm LE

No 19 f (60385) Myopic astigmatism esotropia nystagmus
BW 1450 g GA 30 weeks. OX 35% in incubator for a total of 41 h within the first five days.
At 6 years surgery for cong esotropia glasses for myopic astigmatism Spastic tetraplegia
PEX VRE 6/12 +0 75 –3 5 X 35 VLE 6/12 +0 75 –3.5 X 180
Esotropia of LE nystagmus on lateral gaze OPHTH thin retinal vessels dark pigmentation peripherally in RE

No 20 m (60848) Early myopia
BW 1650 g GA 38 weeks OX short stay in incubator
PEX VRE 6/9 –2 0 –1 0 X 90 VLE 6/6 –2 0
No squint but stereopsis imperfect
TAU AL 22 6 mm RE

No 21 f (30059) Hypermetropic astigmatism esotropia nystagmus tortuosity
BW 1700 g GA 29 weeks? OX nil.
3 years old surgery for esotropia Some intellectual retardation after measles encephalitis at 8 years.
PEX VRE 6/9 +1 0 X 70 VLE 6/18 +1.5 X 115
Lat gaze nystagmus esotropia OPHTH extreme tortuosity
TAU AL 21 8 mm

No 22 m (30785) High hypermetropia tortuosity
BW 1200 g GA <28 weeks. OX 40% in incubator for 4 h by funnel 3 days
Spastic paraplegia At 4 years glasses for hypermetropia
PEX VRE and VLE <6/9 +8 0
Binocularity intact with glasses strands of pup membrane
OPHTH extreme tortuosity foveal reflexes not distinct
TAU AL 20,5 mm RE

No 23 m. (31466) Retinal tortuosity
BW 1500 g GA 28 weeks. OX 40% in incubator for 8 h
PEX VRE >6/6 +0 25 VLE >6/6 +0.5
OPHTH extreme tortuosity

No 24 m. (31602) Retinal tortuosity
BW 1350 g GA 29 weeks. OX 40% in incubator for 6 h by funnel 10 days.
PEX VRE 6/6 +0.5 VLE 6/6 +1 0
OPHTH pale fundi extreme tortuosity

No 25 m (50747) Hypermetropia retinal tortuosity
BW 1850 g GA 34 weeks. OX 40% in incubator for a total of 27 h within the first five days. Exchange transfusions (Rh immun.)
Behavioural difficulties at school.
PEX VRE 6/6 +1 5 VLE 6/6 +2 0
Epicanthus. OPHTH extreme tortuosity

No 26 f (61595) Hypermetropic astigmatism retinal tortuosity
BW 1400 g GA 28 weeks. OX 35% in incubator for 11 h.
PEX VRE >6/12 +1 5 +1 0 X 90 VLE >6/9 +1.5 +1.0 X 90
OPHTH Inverse vessel emergence large physiological cups extreme tortuosity

No 27 f (62103) Retinal tortuosity
BW 1650 g GA? OX 35% in incubator for 2 h. Exchange transfusion.
PEX VRE and VLE >6/6 +0.25
OPHTH pale fundi extreme tortuosity

No 28 m (30910) Infantile glaucoma (unilateral Sturge Weber)
BW 1800 g GA 30 weeks. OX 40% in incubator for 2 h
"Naevus flammeus" on right side of the forehead and including the right upper eye lid. Behavioural difficulties. EEG dysrhythmia. No intracranial calcifications (X-ray)
PEX VRE 6/12 +1 0 VLE 6/6 +1 25
Distended vessels also in the bulbar conjunctiva and episclera of RE (but no angiomas in the fundi) A mucosal haemangioma was seen in the mouth and a cutaneous (capillary) one on the back Applanation tonometry 38 mm Hg of RE 14 mm Hg of LE Glaucomatous defects in the visual field of the RE and pathological cupping of disc otherwise normal OPHTH
TAU AL 22 5 mm RE 21 4 mm LE Axial chamber depth 4.2 mm RE 3.6 mm LE Transverse corneal diameters 12.5 mm RE 11.5 mm LE
The glaucoma and the relative buphthalmos of RE was a new discovery antiglaucomatous surgery has been performed

No 29 m. (61074 B) Tapetoretinal degeneration?
BW 2000 g GA 33 weeks. OX 35% in incubator for 71 h
(Twin A f BW 1500 g normal eye status at PEX)
PEX (1) VRE >6/9 +0 5 VLE <6/6 +0 75
No squint but reduced stereopsis. Normal colour sense (Ishihara Nagel) OPHTH normal.
PEX (2) VRE and VLE 6/18 three years later
Intermittent esotropia binocularity score lower than at PEX (1) visual fields concentr narrowed hemeralopia at adaptometry ERG b-wave 0 25-0.35 mV OPHTH still no significant evidence of retinal dystrophy
EEG audiometric and neurological assessments normal.

No 30 m. (30036 B) Post traumatic anophthalmia on the left.
BW 1400 g GA 36 weeks. OX 40% in incubator for 1 h by funnel 24 h.
(Twin A m BW 2200 g normal eye status at PEX)
Behavioural and educational difficulties. 10 years old enucleation of LE after perforating trauma.
PEX VRE 6/4 5 +0 75 OPHTH normal.

No 31 m. (50990) Congenital cataract nystagmus esotropia
BW 1150 g GA 36 weeks? OX 40% in incubator for 7 h by funnel 60 h.
No family history of early cataract Ocular media described as clear at the age of 1 month but zonular cataracts evident at four months. Repeated discussions Mentally rearded Educated at "Refsnæsskolen"
PEX VRE 1/18 +10 0 (but <3/60) VLE hand movements Esotropia voluntary abduction of LE impossible nystagmus
OPHTH red fundus without visible details
TAU AL 22 mm RE and LE vitreous opacities no evidence of RD

No 32 m (31497) Anterior polar cataract of RE hypermetropic astigmatism
BW 3500 g Born at term.
PEX VRE and VLE 6/6 +1 0 +1 0 X 90
Axial fusiform cataract in ant third of right lens.
OPHTH normal, no optic distortion by cataract
TAU AL 23 1 mm RE 23 4 mm LE Lens thickness 3 8 mm RE 3 6 mm LE

No 33 m (50101 B) Coerulean cataract hypermetropic astigmatism
BW 2100 g GA 37 weeks OX 40% in incubator for 18 h by funnel 24 h
Mentally deficient (with epilepsy and brain atrophy at PEG the same applies to twin A m BW 1950 g)
PEX VRE 6/9 +2.5 +1.5 X 105 VLE 6/6 +2.5 +1.5 X 75
Intermittent esotropia Punctate coerulean cataract bilat

Nos. 34 and 35 both f (60445 A and B) Coerulean cataract
Twins of BW 1900 and 1800 g GA 35 weeks OX nil
PEX VRE and VLE 6/6 +1 0
Punctate coerulean opacities posteriorly in both lenses presenting no obstacle to vision.

No 36 f (61064) Hypermetropic astigmatism coerulean cataract
BW 1850 g GA 38 weeks. OX 35% in incubator for 19 h
PEX VRE 6/6 +1 0 +1 0 X 110 VLE 6/6 +1 0 +1 0 X 75
Fine coerulean dots posteriorly in both lenses visually insignificant
TAU AL 21 1 mm RE lens thickness 3.6 mm RE

No 37 f (32201) Posterior polar cataract (spurious?) of RE
BW 1700 g GA 36 weeks. OX 40% in incubator for 3 h
PEX VRE >6/9 +0.5 VLE <6/9 +0.5
Binocularity intact except for optimal stereopsis annular grey opacity centrally on post lens surface of RE OPHTH medium tortuosity
TAU AL 23 mm of both eyes.

No 38 m (41801) Posterior polar cataract (spurious) of RE
BW 1700 g GA 32 weeks. OX 35% in incubator for 17 h.
PEX VRE and VLE 6/4.5 +0 75
Flat posterior polar opacity in lens of RE
TAU AL 23 8 mm RE

No 39 m (61757 A) Esotropia posterior polar cataract (spurious) of RE
BW 1700 g GA 34 weeks. OX 35% in incubator for 25 h 30% 24 h.
Congenital squint (like twin B) – but no ophthalmic examination before the age of 8 years.

PEX VRE 1/36+2.5 VLE 6/4.5+2.0
Eso- and hypertropia. Opacity (considered visually insignificant) in post. lens cortex of RE. OPHTH normal.
TAU AL 22.9 mm RE

No 40 f. (41867) Amblyopia of LE, posterior polar cataract (spurious) of LE
BW 3250 g. Born at term. OX nil.
Hairy naevi of chin and of left leg. Amblyopia and unilateral cataract diagnosed at the age of 7
PEX VRE >6/6+1.25 VLE <6/36+1.0
No squint in cover tests, but suppression of LE in all sensory binocular tests. Strands of pup. membrane bilat., annular opacity (considered visually insignificant) in post. lens cortex of LE. OPHTH normal.
TAU AL 23.6 mm RE, 23.2 mm LE, axial chamber depths equal (3.4 mm), but left lens (4.3 mm) axially thicker than the right (3.8 mm)

In addition Case 41 with congenital cataract (actually belonging to, but *not* included in the present material, because he was not on my list during the study period, cf. p. 23). The results in this case would have further weighted the premature group in several of the above chapters (on visual acuity, lens changes, binocularity, malformations, nystagmus).

No 41 m. (60038) Idiocy, congenital cataract, amaurosis.
BW 1500 g. GA 32 weeks. OX 35% in incubator for 7 h, 25% 25 h.
Family history: several cases of epilepsy and of mental deficiency
Congenital cataract observed 8 days after birth, several discissions soon after
VBE light perception? OPHTH red retina, not detached
Diagnoses (a) general mental deficiency (idiocy), brain atrophy, symptomatic epilepsy and
(b) ophthalmic amaurosis, esotropia, hypertelorism, nystagmus.